

July 2012

NIEHS Spotlight



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[Trading a pipet for a pen — fellow pursues career in medical writing](#)

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Science Notebook



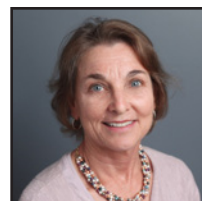
[Johns Hopkins researcher gives Distinguished Lecture](#)

For researcher Rachel Green, Ph.D., who spoke at NIEHS June 12, understanding the intricacies of translation provides the ultimate in scientific investigation.



[NIEHS experts speak at EU Conference on Endocrine Disruptors](#)

NIEHS/NTP Director Linda Birnbaum, Ph.D., opened the European Union Conference on Endocrine Disruptors June 11 in Brussels with her keynote presentation.



[Prenatal chlorpyrifos exposure alters brain structure, affects IQ in children](#)

A new NIEHS-funded study reports that when a pregnant woman is exposed to a commonly used pesticide, her child's developing brain may be damaged.



[Connecting the dots in Parkinson's disease](#)

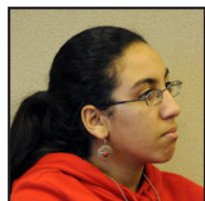
NIEHS gathered twenty leading experts June 7-8 at a Parkinson's Disease Premotor Symptom Symposium to explore prevention, early diagnosis, and treatment.

NIEHS Spotlight



[Public radio features Birnbaum public health message](#)

Public Radio International broadcast an interview with NIEHS/NTP Director Linda Birnbaum, Ph.D., June 8, as part of its popular "Living on Earth" series.



[Workshop challenges high school students with a call to action](#)

Students in the second annual NIEHS/EPA Climate Change Workshop June 11-15 got something more than they might have expected from their learning experience.



[Resnik book tackles ethical issues in environmental health](#)

NIEHS Bioethicist David Resnik, J.D., Ph.D., is the author of a thought-provoking new book appropriately titled "Environmental Health Ethics."



[NICEATM seeks comment on draft plan for 2013–2017](#)

NTP interagency groups instrumental in developing alternative toxicological methods for safety testing are taking public comments on a draft five-year plan.



[SRP scientist Brian Jackson engages his community about arsenic](#)

Jackson and colleagues attended an informal gathering June 20 at a popular restaurant in Concord, N.H. for a Science Café discussion about arsenic in drinking water.

Science Notebook



[Transcription factor binding dominates talks at minisymposium](#)

A cast of scientists at the forefront of 21st century techniques was on hand at NIEHS May 29-30 for a pair of half-day symposia.



[NIEHS researchers publish in scientific video journal](#)

NIEHS stem cell biologists complemented their findings with a video demonstrating the procedures they used in their experiments.



[Pollution and obesity impact asthma control in seniors](#)

A new study, funded in part by NIEHS, explores the effects of traffic pollution and obesity on the growing number of asthmatics in the U.S. who are 65 or older.



[Study links house dust with high risk of exposure to flame retardant chemicals](#)

A new NIEHS-funded study of exposure to polybrominated diphenyl ethers found that toddlers have a significant amount of exposure from house dust.



[Confronting the issue of heritability in large-scale genetic studies](#)

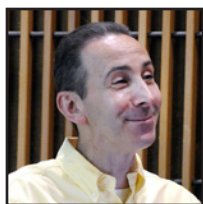
Organized by NIEHS Biostatistics Branch researchers, a symposium May 24-25 focused on "Emerging issues in analysis and design of large scale genetic studies."



[Workshop on informed risk assessment ponders new directions](#)

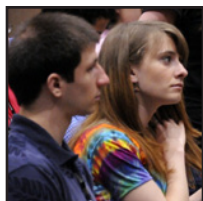
Emerging scientific advances could transform the way scientists analyze the risk of toxic substances to humans, allowing both more efficient and more exact risk assessments.

Inside the Institute



[Zeldin welcomes 2012 summer interns to NIEHS](#)

High school and college students from across the country gathered in Rodbell Auditorium for the June 14 kickoff of the 2012 NIH Summer Internship Program at NIEHS.



[Career exploration panel gives advice to summer interns](#)

Participants of this year's NIH Summer Internship Program attended a question-and-answer style career panel June 19 with five of environmental health's brightest minds.

Calendar of Upcoming Events

- **July 3**, in the Executive Conference Room, 12:00-1:00 p.m. — Receptor Mechanisms Discussion Group, featuring Monte Willis, M.D., Ph.D., addressing "The regulation of nuclear receptors by the ubiquitin proteasome system"
- **July 5**, webinar and in Keystone 2128, 1:00-2:00 p.m. — Superfund Research Program [Trainee Webinar Series](#), webinar [registration](#)
- **July 9**, in Keystone 1003AB, 8:30 a.m.-4:30 p.m. — Genes, Environment, and Health Initiative trainees' meeting
- **July 10-11**, in Rodbell Auditorium — July 10, 8:30 a.m.-5:00 p.m., July 11, 8:30 a.m.-12:30 p.m. — Outstanding New Environmental Scientist Symposium
- **July 12**, in Rall F193, 11:00 a.m.-12:00 p.m. — Laboratory of Toxicology and Pharmacology Seminar Series, featuring Sailesh Surapureddi, Ph.D., topic TBD
- **July 23-24**, in Rodbell Auditorium, 8:00 a.m.-5:30 p.m. — Breast Cancer and the Environment Research Program Integration Meeting
- **July 26**, in Rodbell Auditorium, 9:00 a.m.-12:00 p.m. — NIH Summer Internship Program Poster Session
- View More Events: [NIEHS Public Calendar](#)

Science Notebook



[NTP board supports systematic review, new carcinogen concepts](#)

The literature-based analysis capabilities of the National Toxicology Program took center stage during the NTP Board of Scientific Counselors meeting June 21-22 at NIEHS.



[This month in EHP](#) Audio

This month's feature stories in Environmental Health Perspectives tackle the timely issues of fracking and replacements for toxic chemicals.

Extramural Research

[Extramural papers of the month](#)

- [Gene variants linked with faster Parkinson's disease progression](#)
- [Cardiovascular effects of Beijing Olympics air pollution reduction](#)
- [Environmental exposures influence behavior of later generations](#)
- [Semiconducting properties of nanoparticles linked with oxidative damage](#)

Intramural Research

[Intramural papers of the month](#)

- [Pol II pausing modulates basal gene expression in signal transduction cascades](#)
- [Clustered mutations attributed to body's natural defenses](#)
- [STAT6 and LRP1 polymorphisms are associated with food allergen sensitization in Mexican children](#)
- [Socioeconomic adversity in early life impacts the future risk of rheumatoid arthritis](#)

NIEHS Spotlight

NIEHS and partners issue challenge to innovators

By Cindy Loose

Imagine if people could know, in real time, what pollutants they were being exposed to and what those pollutants were doing to their bodies.

A competition to build a mobile device that would do just that was announced June 6.

The challenge, issued to tech savvy innovators, is to create a personal sensor system, small enough to be worn or carried, that measures both air pollution and the physiological responses of the individual carrying it. Those who accept the challenge, which includes \$160,000 in prize money, are also required to have a plan for making the resulting data available, without revealing individual identities, to researchers, public health institutions, and other interested parties.

The My Air, My Health Challenge, part of the Challenge.gov program, was announced during a health technology forum by NIEHS/NTP Director Linda Birnbaum, Ph.D., and Glenn Paulson, Ph.D., science advisor at the U.S. Environmental Protection Agency (EPA). The Challenge.gov program introduces a new vehicle for pursuing innovation, whereby agencies pay for results rather than funding research.

“Grants fund the proposals that are most likely to succeed, but challenges give the prize to someone who has already achieved success,” said Birnbaum. “These challenges lead to attracting outside investment to an area that’s been a federal priority.”

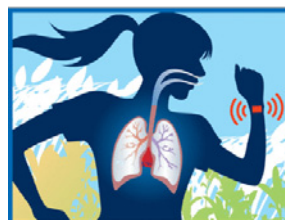
While a successful sensor will be valuable to individuals and specific communities concerned about pollutants, the collective data will be important to scientists who study the relationships between pollutants and diseases. While links to many diseases are already known, scientists face huge barriers in determining what pollutants an individual or group has been exposed to, when, and at what levels.

“If we can detect what a person is exposed to in their environment and then measure how their body responds, we can begin to understand how to prevent certain diseases,” Birnbaum said.

The device being sought would improve on existing fixed sensors, such as those that monitor emissions in a factory, by being portable and adding a feature that measures physiological responses.



For Birnbaum, developing personalized monitors that link environmental exposures and individual physiological responses is key to personalized medicine and better understanding differential host response. (Photo courtesy of Steve McCaw)



**My Air
My Health**

U.S. Department of Health and Human Services
U.S. Environmental Protection Agency

Measuring the body's response to pollutants

While the possibilities for measuring physiological responses to pollutants are infinite, the initial device will most likely measure cardiac and respiratory responses, said NIEHS Senior Advisor Allen Dearry, Ph.D., who manages the My Air, My Health Challenge. The health measurements may include things such as blood pressure, heart rate, some measure of lung capacity, and galvanic skin response, a measure of the electrical conductivity of skin, which can change in response to stress.

Devices entered in the competition must be able to measure airborne pollutants, including chemicals and/or particulates.

Engineers, people familiar with fixed sensors, and mobile software experts are among those expected to compete as individuals or teams, but the competition is open to anyone in the U.S. The deadline for entries is October 5.

As many as four finalists will receive \$15,000 each in phase one of the competition. The winner of phase two, which requires a small-scale, proof-of-concept project, will be awarded \$100,000.

In addition to health and environmental research groups, the device will be useful to community groups concerned about localized pollution and even individuals, said NIEHS program administrator David Balshaw, Ph.D., who is in charge of technical input for the challenge. "This is like 'Field of Dreams,'" he added. "We believe if we make it, they will come."

The My Air, My Health Challenge is sponsored by NIEHS, the EPA, and the U.S. Department of Health and Human Services Office of the National Coordinator for Health Information Technology. The announcement was made at a forum in Washington, D.C., sponsored by the [Health Data Initiative](#), a public-private collaboration that encourages innovators to develop and use health data applications to improve medical outcomes.

This is the first challenge issued by NIEHS, and the first joint challenge in which the National Institutes of Health has partnered with other agencies. Further details about the competition can be found on the NIEHS Challenges [Web page](#).

(Cindy Loose is a contract writer with the NIEHS office in Bethesda, Md.)

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NIEHS-IOM webinar to analyze Rio+20 declaration

By Cindy Loose

For more than a year, NIEHS has been working to make human health an integral part of an international agreement on sustainable development.

Those efforts culminated in June, when thousands of participants and others gathered in Rio de Janeiro for the Rio+20 United Nations Conference on Sustainable Development. The results of the conference, including an expected declaration of intent for action, will be analyzed this month during a webinar sponsored by NIEHS and the Institute of Medicine (IOM).

Sustainability and health

“Sustainable development is a widely shared goal, and our message has been that human health is both a driver of sustainable development and an indicator for judging success or failure,” said NIEHS Senior Advisor for Public Health [John Balbus, M.D.](#), who has led NIEHS efforts to ensure that health was central to conference discussions and decisions.

“We know that making the planet healthier goes hand in hand with making people healthier,” Balbus added. “Making that goal a reality is our ultimate mission.”

In initially setting the goal of re-energizing global development, and in a sustainable way, the U.N. created a framework for decisions around seven topics — jobs, energy, cities, food, water, oceans, and disaster readiness.

Although health did not make the list, it is inextricably linked to every issue, said Balbus, who helped launch a number of activities to make those links explicit and provide guidance about how to incorporate health into actionable goals for the world community.



Balbus leads NIEHS efforts on [climate change](#) and [human health](#). In this capacity, he serves as HHS principal to the U.S. Global Change Research Program. (Photo courtesy of Steve McCaw)

Behind the scenes with WHO

In partnership with the World Health Organization (WHO), NIEHS supported a meeting of experts in Geneva who produced six briefing documents that made the case for human health as a critical element of the issues being discussed. The briefing documents also developed a set of indicators, based on health outcomes, for monitoring progress towards the goals.



RIO+20
United Nations
Conference on
Sustainable
Development

The briefing paper on energy, for example, noted that nearly two million deaths, annually, are due to household air pollution from stoves fueled by coal and rudimentary biomass. About 1.3 million deaths, per year, are attributed to ambient air pollution in cities. Additionally, in some developing countries, over one-half of health care facilities lack reliable electricity, with some having no electricity at all.

The briefing paper then set out core health indicators to be used to monitor progress in sustainable energy access. For example, reducing rates of disease attributable to indoor and outdoor pollution would provide evidence of achievement towards the goal of moving towards sustainable energy. An increase in the proportion of health care facilities with reliable electricity would be another measure.

The briefing documents also point out crosscutting issues requiring further discussion. For example, the paper on energy notes that energy use is a primary driver of climate change and that substantial health benefits would be derived from mitigating global warming.

NIEHS partners in global health

The NIEHS-sponsored IOM Roundtable on Environmental Health Sciences, Research, and Medicine hosted a [webinar](#) with the Pan American Health Organization that highlighted the interactions between health and sustainable economic growth.

NIEHS has also been working with the U.S. Department of State, the White House, and the U.S. Department of Health and Human Services (HHS) Office of Global Affairs to include environmental health concerns in the U.S. government positions at Rio+20.

An article, making the case for using the conference as a crucial opportunity to place environmental health at the forefront of the sustainable development agenda, was written by Balbus and intern Gregg Furie, and published in *Ciência & Saúde Coletiva* (Collective Science and Health), a prestigious Brazilian public health and policy publication, to coincide with the conference.

For more information on Rio+20, visit <http://www.uncsd2012.org/>.

Citation: Furie GL, Balbus JM. 2012. Global environmental health and sustainable development: the role at Rio+20. *Ciênc Saúde Coletiva* 17(6):1427-1432.

(Cindy Loose is a contract writer with the NIEHS office in Bethesda, Md.)

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Presentation details community involvement in environmental public health

By Brant Hamel

Community outreach and engagement veteran Andrea Hricko, of the University of Southern California (USC), delivered a presentation May 24 at NIEHS, focusing on effective collaboration between researchers and community members.

“The community is concerned about environmental health risks related to international trade through the ports of Los Angeles and Long Beach,” Hricko explained. “These are the largest ports in America and are often described as the economic engine of Southern California, with 40 percent of the entire nation’s goods transported through their facilities.”

In her talk, titled “Responding to Community Concerns on Environmental Public Health: Advancing the Scientific Research, Translation, and Policy Agenda,” Hricko detailed the progress that has resulted from the effective engagement of researchers with community members, but stressed that much work remains to be done. Liam O’Fallon, program analyst in the NIEHS Division of Extramural Research and Training (DERT) at NIEHS, hosted the presentation, which was part of the DERT Keystone Science Lecture Seminar Series.



Hricko told her audience that community involvement has helped shift the policy debate about traffic pollution and transportation projects to make the goods movement industry accountable, by taking into consideration the health and environmental impacts from the multiple sources of air pollution. (Photo courtesy of Steve McCaw)

Hricko is a professor at the Keck School of Medicine at USC and heads the Community Outreach and Engagement Core (COEC) at the NIEHS-supported Southern California Environmental Health Sciences Center, directed by Frank Gilliland, M.D., Ph.D. The goals of the COEC are to insert health into the transportation agenda, by sharing Center research findings, strengthening the capacity of the public to understand environmental health, and fostering a network of concerned residents and stakeholders focused on air pollution in the harbor area (see text box).

Positive outcomes of community involvement

Community-engaged research has led to several notable successes, such as the inclusion of research findings into environmental impact studies prepared for port, rail yard, and freeway expansion projects; changes in the idling rules for trucks going in and out of the port; and education of California lawmakers on the health benefits of prohibiting new schools from being situated within 500 feet of a major transportation corridor, which resulted in a state law. However, given the projected growth of the ports, much work remains to be done. For example, new schools cannot be situated close to a major highway, yet there is no restriction on new or expanded highways or rail yards being built next to existing schools.

Hricko noted that some of the advantages of community-academic partnerships include increased understanding of, and connection to, the science by community members; a better awareness of the social justice implications by academics in their research; and more effective advocacy campaigns by community groups that had developed the necessary skills to explain the scientific basis of their concerns to policymakers. Hricko concluded her talk by observing that the successful model of community-academic partnership and outreach that she helped develop at USC is just one of many efforts that are part of the NIEHS Partnerships in Environmental Public Health network that have been well positioned to address other environmental health concerns, such as the Gulf oil spill and hydraulic fracturing.



The ports are big and getting bigger, estimated to double within the next five years. People in the area live, work, learn, and play exposed to high levels of traffic emissions from nearby roads, rails, and docks. (Photo courtesy of John Schelp)



The ports' transportation corridors stretch from Long Beach to East Los Angeles, where pollution from trucks, ships, trains, and other diesel-powered sources poses health concerns for residents and students in homes and schools adjacent to the docks and highways. (Photo courtesy of John Schelp)



USC held community forums in 2001, 2005, and, most recently, in October 2011, drawing capacity crowds of residents, many of them concerned parents. (Photo courtesy of John Schelp)

For more information about the community-engaged research conducted by Hricko and her colleagues, refer to the “Community-Based Participatory Research: A Strategy for Building Healthy Communities and Promoting Health through Policy Change” [report](#). For more information on goods movement, see Hricko’s articles in *Environmental Health Perspectives* titled “[Global Trade Comes Home: Community Impacts of Goods Movement](#)” and “[Guest Editorial: Ships, Trucks, and Trains: Effects of Goods Movement on Environmental Health](#).”



During opening remarks at the 2011 forum, NIEHS/NTP Director Linda Birnbaum, Ph.D., at podium, was joined by panelists, including USC representatives Gilliland, front left, and Hricko. (Photo courtesy of John Schelp)

(Brant Hamel, Ph.D., is a postdoctoral fellow in the NIEHS Molecular Endocrinology Group.)

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Olden named to head EPA programs

By Eddy Ball

In a May 31 email to agency staff, U.S. Environmental Protection Agency (EPA) official Lek Kadeli announced the appointment of NIEHS Director Emeritus Ken Olden, Ph.D., to head two high-profile programs.

Kadeli, who is acting assistant administrator of the EPA Office of Research and Development, wrote that Olden will direct both the [National Center for Environmental Assessment \(NCEA\)](#) and the [Human Health Risk Assessment Program \(HHRA\)](#), effective July 2. Kadeli wrote that he expects Olden to make important

NIEHS town meetings spur involvement

Hricko detailed how the Center is a national leader in research on the health effects of air pollution, and she said that its outreach program’s focus on goods movement, or transport of containers with products inside them, grew out of community concerns raised at a 2001 USC-NIEHS town hall meeting in Los Angeles. At the meeting, residents spoke about the rapid growth at the ports, and the concomitant pollution from the trucks and locomotives transporting goods arriving from Asia. As one example of the impact of increased levels of transportation, Hricko described a school near a rail yard where 500 trucks per hour pass by and where 28 percent of the students already have asthma. She noted that the rail yard is proposed for expansion, despite the opposition of local residents.

Hricko explained that one approach used by the Center, to ensure that community members are actively involved in air pollution research, is the creation of neighborhood assessment teams, or A-Teams. These are teams of USC-trained community members who track data, such as the number of big rig trucks passing a school in a given time period and the concentration of ultrafine particles measured using real-time monitoring devices. A-Team members are often parents of children affected by asthma and are chosen based on their community leadership capabilities. Talented A-Team members have gone on to serve as permanent staff members on projects.

contributions to the programs. “Ken comes to EPA with a strong legacy of promoting scientific excellence in environmental health.”

Olden served as director of NIEHS and NTP from 1991 to 2005, when he left his leadership role and became a lead researcher in the Laboratory of Molecular Carcinogenesis Metastasis Group. In 2008, he accepted an offer from the City University of New York (CUNY) to be founding dean of the new School of Public Health at Hunter College, a unique program with an urban public health focus.

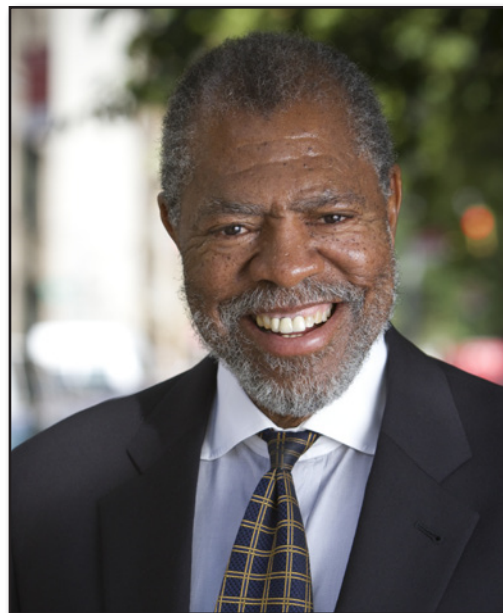
Olden led the development of the curriculum and recruitment of 26 tenure-track faculty. In early 2011, Olden moved with the school from its temporary home to a new eight-story, 147,000-square-foot green building in East Harlem. Last summer, the [Council on Education for Public Health \(CEPH\)](#) announced its accreditation of the [CUNY School of Public Health \(SPH\) at Hunter College](#) for a five-year term extending to July 1, 2016.

From the outset, Olden saw his role at CUNY as a three-year commitment to get the new school underway. “Once the transition to our new location is complete, my task [here in New York] will be over,” Olden said when accreditation was announced.

According to a story about his appointments in the June 8 issue of [Inside EPA](#), Olden will oversee efforts to revamp the agency’s Integrated Risk Information System (IRIS), which produces many of EPA’s most influential and sometimes controversial risk assessments. Industry has complained that the assessments are overly conservative, public health advocates have complained about delays, and last year the National Academy of Sciences issued a critical report outlining recommendations for improving IRIS.

Olden succeeds NCEA Acting Director Rebecca Clark, who served for two years following the departure of the program’s long-time former director, Peter Preuss. Olden’s primary assignment will be at NCEA headquarters in Washington, D.C., although Research Triangle Park, N.C.-based regional director John Vandenberg said he anticipates Olden will also have office space at the facility in N.C.

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When Olden came to NIEHS in 1991, he said his goal was to raise the Institute’s image among key officials in the executive and legislative branches, to make the NIEHS a prime-time player in environmental health nationally and worldwide. (Photo courtesy of CUNY)

Trading a pipet for a pen — fellow pursues career in medical writing

By Sheila Yong

“Writing has always been my passion, but I wasn’t sure which career path was the right one for me,” said Emily Zhou, Ph.D., a former NIEHS research fellow who recently moved on to her new position as a medical writer at [PPD](#). “NIEHS provided the support I needed to figure that out.”

Zhou obtained her Ph.D. in pharmacology from the University of North Carolina at Chapel Hill, and came to NIEHS in April 2009 as a research fellow working with [Stephen Shears, Ph.D.](#), in the Laboratory of Signal Transduction. Shears was very supportive of her interest in writing and offered her opportunities to compose commentaries on published literature on Faculty 1000. Moreover, her stint with the Environmental Factor broadened her experience in writing for a wider audience. “I’m very appreciative of opportunities available writing for the Environmental Factor. I was able to build and showcase a portfolio of writing samples.”

In her new position, Zhou provides feasibility services to pharmaceutical clients who wish to conduct clinical trials by analyzing existing data and infrastructure, and subsequently making recommendations as to whether the trials are feasible or not. “I wasn’t sure what I was getting myself into,” she laughed, when asked how her current position is different from her research role at NIEHS. Her current job is fast paced, and having a short turnaround time for her assignments has been testing her ability to think on her feet. “I have a week to analyze data and write an average 40-page report, and it does get very intense. However, I enjoy the fact that I am working with something different every day,” she commented.

Career development and networking

Apart from her research responsibilities at NIEHS, Zhou was actively involved with the NIEHS Trainees Assembly (NTA) and was a co-chair for the [2011 Biomedical Career Fair](#). Her involvement with the NTA subcommittees gave her the opportunity to meet people outside the lab and in other organizations, and exposed her to various managerial and organizational tasks, all of which are crucial to her current job. Time management skills played a big role as well, as she had to balance her research with her efforts in building her professional network. She also acknowledged that the analytical and critical thinking skills she learned as a graduate student and research fellow help her tremendously in her role as a medical writer, where she often has to analyze data and information on various topics that are outside her field of training.

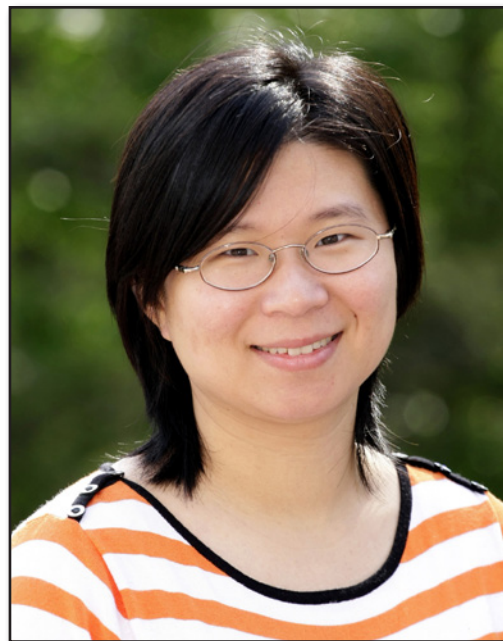
Zhou found her job online, but with a twist. “Andy was job-hunting too, so we helped each other out,” she said, referring to NIEHS postdoc Andy Seipel, Ph.D., who works in the lab down the hall from hers. Seipel came across this opening online and sent it to her, and the rest is history. Therefore, one piece of advice she has to offer is to form a support group and help one another out.

“Job hunting can be very stressful, and it does help to have another pair of eyes out there to make sure that no stone is left unturned,” Zhou said. She also feels that while it is important to make one’s career aspirations a priority, it is also essential to be attentive to changes in the job market trends to ensure higher success in finding a job that suits one’s interests.

At this point, Zhou is unsure about her plans beyond her current position or where it will take her. “But I am very happy where I am,” she smiled.

(Sheila Yong, Ph.D., is a visiting fellow with the NIEHS Laboratory of Signal Transduction Inositol Signaling Group.)

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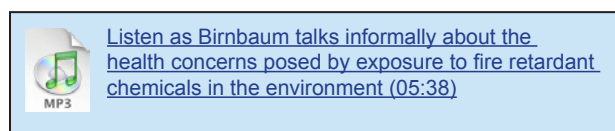


Zhou was active in career development activities at NIEHS and elsewhere in Research Triangle Park, including workshops at the North Carolina Biotechnology Center. As a guest writer for the NIEHS monthly newsletter, she built a portfolio of writing samples on scientific and general topics. (Photo courtesy of Steve McCaw)

Public radio features Birnbaum public health message

By Eddy Ball

Inspired by a new [study](#) from a research team led by NIEHS/NTP Director Linda Birnbaum, Ph.D., Public Radio International broadcast an interview with Birnbaum June 8 as part of its popular “[Living on Earth](#)” series. During the five-minute discussion with host Steve Curwood, Birnbaum addressed concerns about fire retardant chemicals, in a message designed to inform, without unduly alarming, a general audience.



Published online May 31 by Environmental Health Perspectives, the study attracted the attention of “Living on Earth” editors with its findings of detectable levels of the chemical hexabromocyclododecane (HBCD), a brominated flame retardant used in polystyrene foams in thermal insulation and electrical equipment, in 42 percent of food samples from Dallas supermarkets. Fatty foods, such as beef, poultry, fish, and peanut butter, were most likely to contain traces of the chemical. In meats, it was likely the result of bioaccumulation. In peanut butter, the culprit was probably contaminated packaging.

An expert in the field who has published a number of studies about fire retardant chemicals, Birnbaum was careful to strike a balance between communicating her concerns about the chemicals in humans and animals, both in food and from exposure to products treated with fire retardants, and reassuring the audience.

“I think it’s important to stress that the levels that we found are very, very low at this point,” she told Curwood, “and, in fact, that the levels are almost a thousand times lower than what has been considered to be a virtually safe dose for these chemicals.”

As Birnbaum explained, she and others have concerns about potential effects of cumulative exposure on the immune and reproductive systems, as well as on the developing nervous system and in endocrine disruption. While there are certainly appropriate applications for fire retardants, such as in airplanes, she said they are probably not as useful in most of the products where they can be found.

“I think the question we should be asking about some of these flame retardants is, ‘Do we really need them in nursing pillows and baby strollers and baby car seats?’” Birnbaum concluded. “I think that’s really a very important question to ask, whether they really are providing a fire safety benefit in all situations.”

Citation: [Schechter A, Szabo DT, Miller J, Gent TL, Malik-Bass N, Petersen M, Paepke O, Colacino JA, Hynan LS, Harris TR, Malla S, Birnbaum LS. 2012. Hexabromocyclododecane \(HBCD\) Stereoisomers in U.S. Food from Dallas, Texas. Environ Health Perspect; doi:10.1289/ehp.1204993 \[Online 31 May 2012\].](#)



In addition to a host of papers on flame retardant chemicals, Birnbaum has been a keynote speaker at conferences worldwide. (Photo courtesy of the University of Illinois)

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Workshop challenges high school students with a call to action

By Eddy Ball

Students attending the second annual NIEHS/U.S. Environmental Protection Agency (EPA) Climate Change Workshop June 11-15 got something more than they might have expected from their learning experience. Along with presentations by experts, the high schoolers were challenged to reach out to students and faculty at their schools this fall, and given direction in designing effective strategies for raising awareness, by veteran environmental organizer Johanna de Graffenreid of the [Alliance for Climate Education \(ACE\)](#).

To drive home the workshop's call to action, workshop organizers Bono Sen, Ph.D., of NIEHS, and Kelly Leovic of EPA scheduled de Graffenreid as the opening and closing speaker at the workshop. In between de Graffenreid's opening session Monday morning and her course in Project Planning 101, the students heard from, and interacted with, specialists in climate change and health from NIEHS, EPA, and elsewhere, on a range of climate change-related topics ([see text box](#)).

"We learned a lot from last year," Sen said of the debut workshop in 2011 ([see story](#)). "This year, I bet the whole cohort [of students] will engage in follow-up activities." Sen pointed to the addition of more movement and tours to the schedule, as well as the immediacy of much of the workshop content.

According to student evaluations, Sen and Leovic's planning paid off. As one student wrote, "I will pass on my knowledge to members in our environmental club, and this program propelled me to participate in more green programs."

As timely as the evening news

Reinforcing the workshop's call to action was the timeliness of several of the presentations. NIEHS Senior Advisor for Public Health [John Balbus, M.D.](#), discussed efforts by NIEHS and other federal groups to make health a focus of sustainable development efforts underway at the Rio+20 United Nations Conference on Sustainable Development ([see story](#)). "Health is one of those areas where we can really do something about this credible impasse we have on the international scene," Balbus told attendees, as he described the economic benefits of improved health from climate change mitigation.

The students were also treated to a lively presentation June 14 on "The Battle for North Carolina's Coast," by East Carolina University geologist [Stan Riggs, Ph.D.](#), a representative of the N.C. Coastal Resource Commission's Science Panel on Coast Hazards. Riggs discussed his group's position on a possible one-meter increase in

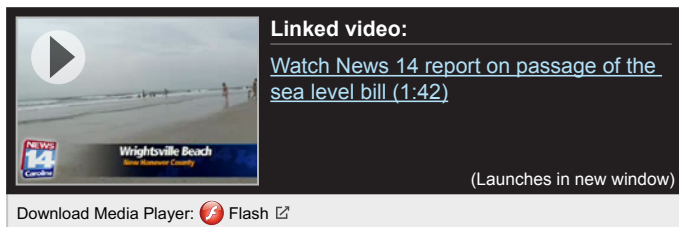


Sarah Hassan of Riverside High School was one of several from Durham County, N.C. schools. A few of the students from more distant schools in Johnston and Guilford counties spent as long as 90 minutes getting to and from the workshop each day. (Photo courtesy of Steve McCaw)



Along with co-organizing the workshop, Sen was also a presenter. She is the EHP science education and outreach program manager and an associate member of the [NIEHS Office of Science Education and Diversity \(OSD\)](#). (Photo courtesy of Steve McCaw)

sea level by 2100, and his opposition to a controversial bill passed June 13 by the N.C. Senate to limit predictions to eight inches for purposes of planning coastal development.



De Graffenreid's closing session June 15 combined timeliness and a call to action, with a module on hydraulic fracturing or fracking. Like Rio+20 and sea level rise on the coast, fracking was in the news that week, as N.C. legislators conferred over different versions of a [bill](#) to legalize the practice in the state. The EPA building in Research Triangle Park (RTP), N.C., where the workshop was held, sits on the edge of a Triassic Basin shale oil deposit that runs from Durham, N.C., to the South Carolina border.

The impact on participants

Students evaluated activities each day and, as the workshop came to a close, they had an opportunity to comment on the entire program. Some participants offered suggestions about how to tweak the workshop schedule and suggested activities, but the students' comments were overwhelmingly supportive of the experience. A majority wrote that they would attend the workshop again, even it didn't feature the modest stipend the program offered this year, which was made possible through funding primarily by Environmental Health Perspectives (EHP).

"[The workshop] completely changed my views," wrote one student. "I had no idea climate change was so urgent." Another student agreed, writing, "[I] learned a lot about the actual science and policies regarding climate change, and I feel more aware and conscious about how my actions affect climate change."

Just as organizers hoped, the students were inspired by the workshop's call to action and emphasis on planning and communication. "I now know a project I can do at my school to help our planet go greener," one participant concluded. Others listed specific projects, including composting, conservation of water and electricity, and installation of solar panels.



Although Balbus gave one of the longer presentations, he kept the students' attention with his outline of the cobenefits that would accrue from mitigating the health impact of climate change, and his ongoing involvement in the international discourse about climate. As one student wrote, "He's really been there." (Photo courtesy of Steve McCaw)



In her introduction of Riggs' talk on sea level change, as well as in her presentations and interaction with students, Leovic's enthusiasm was evident throughout the workshop. Leovic is the manager of the EPA Science, Technology, Engineering, and Math (STEM) program, as well as EPA environmental outreach programs in RTP, and a member of the Environmental Cutting Edge Speakers Series Committee, sponsor of the talk. (Photo courtesy of Steve McCaw)

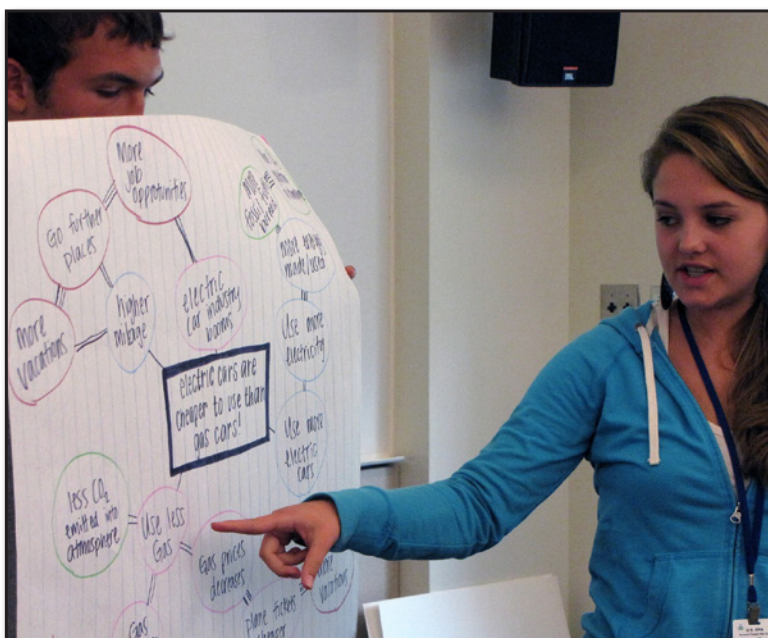
A cast of experts on climate change and health

Along with Sen, Leovic, and the keynote speakers, a number of experts from NIEHS, EPA, and other organizations shared their perspectives during the workshop. The topics ranged from solar cookstoves to the NIH GuLF STUDY. Presenters included the following people:

- **NIEHS volunteers** — public affairs specialist Ed Kang; former postdoctoral fellow Linh Pham, Ph.D.; outreach specialist John Schelp; postdoctoral fellow Jim Aloor, Ph.D.; postdoctoral fellow Kym Gowdy, Ph.D.; NIH Summer Internship Program coordinator Debbie Wilson; and epidemiologist Richard Kwok, Ph.D.
- **EPA volunteers** — remote sensing and geospatial researcher Drew Pilant, Ph.D.; atmospheric modeling researcher Prakash Bhawe, Ph.D.; environmentally preferable purchasing specialist Wanda Allen; air quality planning and standards specialist Meredith Lassiter, Ph.D.; physical scientist Rebecca Dodder, Ph.D.; energy manager Greg Eades; postdoctoral research fellow Tyler Felgenhauer, Ph.D.; environmental specialist Joseph Mangino; outreach specialist Rachel Clark; sustainable building specialist Pete Schubert; analyst Kathy Kaufman; and sustainability advisor Melissa McCullough.
- **Community volunteers** — North Carolina Agricultural and Technical State University professor Manny Reyes, Ph.D.; North Carolina State University professor Ryan Boyles, Ph.D.; Durham Technical Community College instructor Jane Norton; and 2011 climate change workshop participant Kelsey Bennett.



After leading the students on a tour of the NIEHS facility, Schelp, right, talked about environmental research and how it relates to the lives of members of his audience. Schelp is the OSED special assistant for community engagement and outreach. (Photo courtesy of Steve McCaw)



Bennett returned to this year's workshop to discuss her project at Jordan High School in Durham, N.C. She is shown above making a presentation last summer on electric cars. (Photo courtesy of Ian Boudreau and EPA)



Kang created a teamwork exercise for the students based on the Fukushima Daiichi nuclear disaster in March 2011. "If you cross the lines [in the real situation]," he said, "you're dead." (Photo courtesy of Steve McCaw)



The students worked together to move representations of nuclear rods into a protected area. To succeed, two or three people needed to work together to tip the bucket and put the rods where they belonged. (Photo courtesy of Steve McCaw)





De Graffenreid's pace was steady, but informal, as she moved through a description of energy issues, the ACE network, and the kinds of programs students at other schools nationwide have created. She called the students climate communicators and emphasized the value of messaging with a story of self, a story of us, and a story of now. (Photo courtesy of Steve McCaw)




By the end of the week, the students were used to working together on problem-solving activities and looking forward to getting back to their home schools to build environmental awareness projects. Shown above, Willa Chen, center, of Chapel Hill High School, laughed with teammates, as they discussed their projects. (Photo courtesy of Steve McCaw)

Basic Information





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▶ The Maldives are a beautiful group of 1,192 islands in the Indian Ocean. There is a dry season and a wet season, and the weather is very tropical. The main sources of income for this nation are tourism and fishing. The highest point is only 8 feet above sea level.




Do you really want this place to disappear?



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EPA-NIEHS Climate Change Workshop



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▶ **Effects of Climate Change on the Maldives**

One outcome of student collaboration at the workshop was this brochure the students put together to bring home a message about the very real threat to health and wellbeing posed by rising sea levels.

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Resnik book tackles ethical issues in environmental health

By Eddy Ball

NIEHS Bioethicist [David Resnik, J.D., Ph.D.](#), is the author of a thought-provoking new book appropriately titled “Environmental Health Ethics.” The book, which is Resnik’s eighth, is now available from publisher [Cambridge University Press](#), as well as several online booksellers.

Resnik offers readers a method for weighing benefit and harm in a variety of situations, ranging from pesticide use, antibiotic resistance, nutrition policy, vegetarianism, and urban development to occupational safety, disaster preparedness, and global climate change. The book begins by describing the birth of the modern environmental movement inspired by Rachael Carson’s “Silent Spring” in 1962. The debate that ensued over the powerful insecticide DDT, Resnik explained, continues today and involves weighing important human benefits, increased crop yield, and the reduction of diseases transmitted through insects with harm to the environment from damage to wildlife and humans exposed through diet or direct contact.

Striving for a conceptual framework

In this kind of situational decision-making arena, Resnik argues, compromise among people with competing values and interests is essential and unavoidable. Absolute ethical principles give way, because ideological, economic, or religious ethical systems are more likely to alienate opponents than help them to find a middle ground, where competitors who cannot win entirely, at least can end up feeling they have achieved a fair amount of what they need and deserve.

“Another theme of the book is that human health and the environment put a new twist on some of the traditional questions of ethics,” Resnik wrote. These include issues of individual rights and the common good, the moral basis for government restrictions on property rights, and justice, all complicated by their intersection within the context of the environmental policy and environmental health. Within environmental health ethics, there are usually far more than two sides to every issue.

Into this multifaceted ethical battleground, Resnik introduces a conceptual framework that he applies to practical problems related to environmental health, which will be very familiar to readers whatever their background or interests. His goal is ambitious — to make possible decisions and policies, that are consistent and based on evidence and argument, open to public criticism.

Early reviews

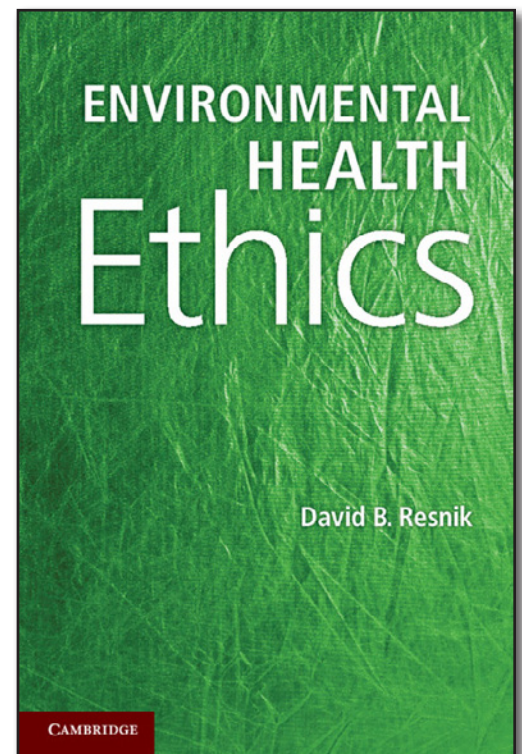
Experts in the fields of environmental health and ethics have applauded Resnik’s insights into the complexities of balancing the benefits to human health and wellbeing with the integrity of the environment. “Resnik has written a wonderful introduction to the field of environmental health ethics,” wrote University of South Carolina professor of philosophy and ethics [Kevin Elliott, Ph.D.](#) “He supplies a wealth of information about the key ethical issues in the field, as well as the science that underlies those issues.”

Describing the new book as an invaluable instructional text, Tufts University professor of urban and environmental policy and planning Sheldon Krimsky, Ph.D., praised Resnik’s systematic approach. “I cannot think of a better book that applies ethics to public health and is informed by the best literature in both fields,” Krimsky wrote. “In his exceptionally lucid analysis, Resnik applies Aristotle’s ‘Doctrine of the Mean’ to applied ethical problems in environmental health, by avoiding excess and deficiency in working out ethical dilemmas.”

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In addition to his books, Resnik has published more than 180 articles on various topics in philosophy and bioethics. (Photo courtesy of Steve McCaw)



Resnik begins by thanking a host of scientific and public health experts at NIEHS for their helpful comments and critiques. (Photo courtesy of Cambridge University Press)

NICEATM seeks comment on draft plan for 2013–2017

By Debbie McCarley and Cathy Sprankle

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) is taking public comments until Aug. 13 on a draft five-year plan developed in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). ICCVAM is an interagency committee of the federal government that NICEATM administers. The plan is available on the [NICEATM–ICCVAM website](#).

The document will provide strategic direction for NICEATM and ICCVAM during 2013–2017. It outlines how, consistent with ICCVAM’s statutory duties and purposes, NICEATM and ICCVAM will contribute to the transformation of safety testing, by fostering and promoting the incorporation of scientific advances and innovative technologies into new improved test methods, and integrated testing and decision strategies.

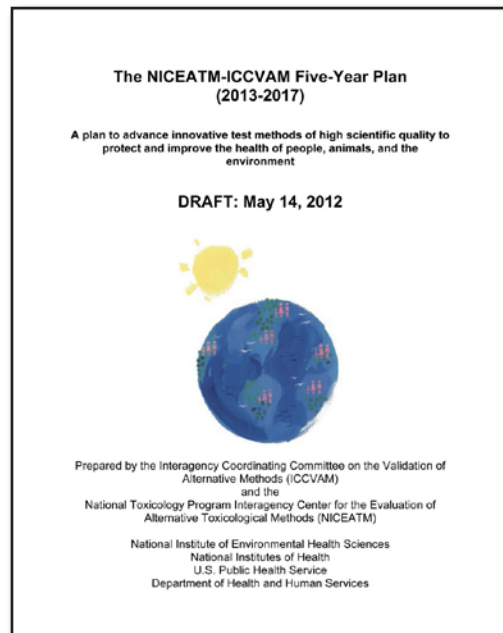
ICCVAM was established to promote development, validation, and regulatory acceptance of new toxicology and safety testing methods. New test methods that take advantage of advances in technology can better characterize the safety and potential hazards of chemicals and chemical products, which in turn can provide better protection of people, animals, and the environment. New test methods also provide the opportunity to use fewer or no animals for chemical safety testing, or to enhance animal well-being, and lessen or avoid pain and distress in those cases where animal testing is still necessary.

In 2008, NICEATM and ICCVAM published a five-year plan for 2008-2012. The plan described ICCVAM’s vision to play a leading role in fostering and promoting the development, validation, and regulatory acceptance of scientifically sound alternative test methods, both within the federal government and internationally.

Responding to the fact that the time period covered by the current five-year plan was coming to a close, last November, NICEATM published a request for comment on development of a five-year plan for 2013-2017. Comments received were considered, as NICEATM worked with an ICCVAM subcommittee in early 2012 to develop the draft plan that was released last month.

“Recent advances in emerging science and technology innovations are driving transformative changes in toxicology and how safety testing is performed,” noted ICCVAM vice chair Joanna Matheson, Ph.D., of the Consumer Product Safety Commission, who is chairing the ICCVAM subcommittee. “For example, data from *in vitro* testing batteries and integrated decision strategies, that consider chemical and toxicological database information, are becoming more important to regulatory decision-making. The next five years will be an essential transition period for NICEATM and ICCVAM in this changing regulatory toxicology environment.”

“In developing this plan, we recognize the need to be able to take advantage of advances in science and technology that will take place over the next five years,” commented Rear Adm. William Stokes, D.V.M., who is director of NICEATM. “We want to best position NICEATM and ICCVAM to promote and help translate the incorporation of new science into improved and innovative test methods that better characterize the safety or hazard of new chemicals and products. These improved methods will better protect people’s health, and are also expected to reduce and replace animal use in testing.”



The draft 2013–2017 Five-Year Plan is available on the [NICEATM–ICCVAM website](#). Those wishing to submit a comment on the plan may do so [via a form on the NICEATM–ICCVAM website](#), or via email to niceatm@niehs.nih.gov, by Aug. 13, so that the advisory committee can consider public comments in their review of the draft plan. The five-year plan will be discussed at the September meeting of the [Scientific Advisory Committee on Alternative Toxicological Methods](#).

(Debbie McCarley is a special assistant to Stokes. Cathy Sprankle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

Call for comments

A notice announcing the availability of the draft plan was published on June 13 in the Federal Register. The draft plan describes four broad strategic opportunities for NICEATM and ICCVAM to foster and promote development, validation, and regulatory acceptance of scientifically sound alternative test methods by the federal government and other organizations.

- Promote the application and translation of innovative science and technology, to develop predictive alternative test methods and efficient and predictive integrated testing and decision strategies.
- Advance alternative test methods and testing strategies, through new evaluation activities for focus areas initially identified in the 2008-2012 five-year plan and new focus areas for 2013-2017.
- Facilitate regulatory acceptance and use of alternative methods, through high-quality test method evaluations and effective outreach and communication.
- Develop and strengthen partnerships with the broad range of ICCVAM stakeholders.

NIEHS and NICEATM invite comments on the draft plan from all ICCVAM stakeholders. In addition, comments are sought on how NICEATM and ICCVAM can most effectively contribute to the evolving transformation of safety testing. Stakeholder comments will be considered in finalizing the draft plan, prior to planned publication in December 2012.

Questions about NICEATM and ICCVAM activities can be addressed to William Stokes, D.V.M., director of NICEATM (see contact information below). Copies of documents mentioned in this update can also be obtained by contacting NICEATM.

Contact Information: niceatm@niehs.nih.gov; phone 919-541-2384; fax 919-541-0947.

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SRP scientist Brian Jackson engages his community about arsenic

By Heather King

On the evening of June 20, Brian Jackson, Ph.D., of the NIEHS [Superfund Research Program \(SRP\)](#) at [Dartmouth College](#), met up with fellow scientists Joseph Ayotte of the U.S. Geological Survey (USGS) and Paul Susca of the New Hampshire Department of Environmental Services (NHDES) for an informal gathering at a popular local restaurant. They were joined by a packed house of Concord, N.H., residents who came to take part in a [Science Café New Hampshire](#) discussion titled “Arsenic In Our Environment: Are Levels Unsafe?” and to learn about the importance of arsenic testing for private wells.

A toxic combination of rock, water, and wells

Arsenic, a deadly poison that kills quickly at high doses, can also cause harm in the parts-per-billion (ppb) range. Long term exposure to low levels of arsenic in drinking water has been associated with a range of health problems from cancer to immune system problems and reproductive defects.

[Jackson](#), director of the Trace Metal Analysis Core facility at Dartmouth, specializes in characterizing inorganic environmental contaminants, such as arsenic, from samples ranging from organic nutrition bars to bedrock. In New Hampshire, [arsenic in bedrock](#) is a big concern, because over half a million of its citizens drink from private wells drilled into and around that rock, and these wells are not regulated or monitored by any state laws or other agencies.

Ayotte, a hydrologist who studies groundwater quality in New Hampshire, can also attest to the troublesome combination of low pH and low oxygen in the water flowing across those rocks that allows it to carry arsenic into drinking wells at levels well above the U.S. Environmental Protection Agency standard of 10 ppb.

Susca, who supervises the NHDES [Drinking Water Source Protection Program](#), knows how much effort goes into keeping the New Hampshire water supply safe. He also understands that informed and active citizens are the key to preventing health issues related to arsenic contaminated private wells.



The panelists sat informally with the audience at The Barley House restaurant, as they answered questions about arsenic and how people can make their families' drinking water safer. Shown, left to right, are Ayotte, Susca, and Jackson. (Photo courtesy of Dartmouth SRP)



The event drew a capacity crowd of people, who enjoyed refreshments while scientists described their field and lab work, as well as resources for learning and doing more about arsenic in well water. (Photo courtesy of Dartmouth SRP)

High-stakes community outreach

Jackson and fellow Science Café panelists were pleased to have this opportunity to come together and demonstrate a common concern for public health, by explaining, directly to community members, the importance of having private wells tested for arsenic. Participating in local, community events of this kind is a major focus of the Dartmouth SRP, which has an active [Research Translation program](#) that sponsors events such as risk workshops and conferences, and has even produced a short film, “In Small Doses: Arsenic,” to inform the community about well water testing.



Bidirectional communication

Bidirectional communication and collaboration between the SRP and federal and state agencies, such as the USGS and NHDES, was clear in the teamwork shown by the panelists, but their ultimate goal was to foster collaboration with the public. Although the science and technology behind the story of well water arsenic involves technical research and complex public policy, the ultimate message is one for the community — “Protect your family. Test your well.”

Effective outreach does more than teach. It gets people to collect samples of their tap water and take them in to be analyzed — the critical step in translating research into improved human health. Several people in attendance also took a survey, providing important information about their well water use that can feed back into the research being done.

Although many scientific programs are measured by prestigious journal publications and conference lectures, and the Dartmouth SRP group can boast plenty of both, this program also has keen insight into the importance of community engagement. In participating in this event, they remind fellow scientists that sometimes a visit to The Barley House restaurant can have a higher impact than any paper.

(Heather King, Ph.D., is an environmental health writer for MDB, Inc., a contractor for the NIEHS Superfund Research Program.)

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Science Notebook

Johns Hopkins researcher gives Distinguished Lecture

By Robin Arnette

Translation, or how living systems assemble proteins, is a complex mechanism that takes place on a cellular structure called the ribosome. For researcher Rachel Green, Ph.D., understanding its intricacies provides the ultimate in scientific investigation. She presented her work during her NIEHS Distinguished Lecture June 12.

Green studies two specific aspects of translation, namely how the ribosome chooses which transfer ribonucleic acids (tRNAs) to add to the messenger RNA (mRNA) template and how newly-formed proteins are released.

Having always been fascinated by questions about the origin of life, Green said examining how RNA stitches amino acids together allows her to see how translation began.

“If we open up the ribosome and take a look inside, all you see is RNA, which gives us confidence that the process must have evolved early on in an RNA world,” Green said. “Proteins came late in evolution as a supplement to make what we know as translation better, faster, and stronger.”

Making a protein

Green gave a brief review of translation, which is the walk of tRNAs along an mRNA. It occurs when a peptidyl-tRNA, or a tRNA that has a string of amino acids attached to it, is positioned over three nucleotides, or codons, on the mRNA. During this initial step of protein synthesis, the peptidyl-tRNA is positioned in the P site of the ribosome. With every round of amino acid addition, the ribosome needs to select a tRNA from solution that corresponds to the codon presented in the neighboring aminoacyl or A site. *E. coli* and most organisms have approximately 40 tRNAs that correspond to 61 codons that code for a particular amino acid. The final three codons, UAA, UAG, and UGA, are stop codons but, instead of being decoded by tRNA, they are recognized by proteins called release factors (RFs).

In bacteria, RF1 and RF2 bind with an energy-producing GTPase molecule called RF3 to terminate translation. In higher organisms, eukaryotic release factor 1 (eRF1) and its GTPase eRF3 do the job. Green stressed that although these proteins have the same names and functions, they are quite different proteins that evolved independently.



Green was elected to the National Academy of Sciences in May and is a professor in the molecular biology and genetics department at Johns Hopkins University School of Medicine, as well as a researcher at the Howard Hughes Medical Institute. She said she plans to use ribosomal profiling to better define what Dom34 and Hbs1 are doing in the cell. (Photo courtesy of Steve McCaw)



According to Hall, Green's work could lead to new breakthroughs in drug design. She said, "Ribosomes are the targets of many antimicrobial agents, so her mechanistic work has obvious clinical implications." (Photo courtesy of Steve McCaw)

Degradation machinery

Preliminary work led Green to think that termination events were closely related to the monitoring of RNA quality, also known as mRNA surveillance. If the RNA has errors in it, the cell wants to get rid of those aberrant messages, because they are toxic. Research by other groups found that two proteins trigger the degradation of a bad message, Dom34 and Hbs1. Surprisingly, Dom34 is an eRF1 homolog and Hbs1 is an eRF3 homolog.

“Since it had just been shown, genetically, that Dom34 and Hbs1 are important for targeted mRNA decay in cells, we wanted to see what they would do if they encountered a ribosome,” Green added.

One of Green’s graduate students reconstituted translation *in vitro*, by using purified yeast ribosomal subunits, mRNAs, tRNAs, and minimal initiation, elongation, and termination factors. After doing kinetic analyses, he ran the products on a native gel and found that Dom34 and Hbs1 trigger the release of peptidyl-tRNA.

Further work determined that Dom34 and Hbs1 are termination-like factors that don’t catalyze termination, but are involved in recycling. Recycling is a vital step in translation that results in the dissociation of ribosomal subunits after a full-length protein is released.

This dissociation allows for normal initiation and subsequent rounds of translation. Scientists knew that bacteria used ribosome recycling factor for this action, but since eukaryotes lacked an apparent homolog, it wasn’t clear how this process took place in higher organisms. Green’s investigations shed new light on the topic.

Laboratory of Structural Biology researcher Traci Hall, Ph.D., hosted the seminar and lauded Green’s work in the field. Hall said, “Her exquisite biochemical studies have exposed novel aspects of protein translation and genome regulation, including quality control of protein synthesis.”

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Transcriptional Responses to the Environment Group head Karen Adelman, Ph.D., offered several suggestions during the question and answer session. (Photo courtesy of Steve McCaw)



Green’s seminar brought scientists from a variety of disciplines together. From right to left, are William Beard, Ph.D., and Nisha Cavanaugh, Ph.D., from the Laboratory of Structural Biology, and summer student Forrest Ashworth, Jacqueline de Marchena, Ph.D., and Patricia Jensen, Ph.D., from the Laboratory of Neurobiology. (Photo courtesy of Steve McCaw)

NIEHS experts speak at EU Conference on Endocrine Disruptors

By Eddy Ball

NIEHS/NTP Director Linda Birnbaum, Ph.D., opened the [European Union \(EU\) Conference on Endocrine Disruptors](#) June 11 in Brussels with her keynote presentation on “Endocrine Disruption: Where Do We Go From Here?” The conference, which was sponsored by the European Commission, attracted more than 350 attendees.

Joining Birnbaum in the program's exploration of current challenges and policy were NIEHS Health Scientist Administrator Jerry Heindel, Ph.D., and grantee Tracey Woodruff, Ph.D., as well as researchers and policy experts from the U.S. and EU. The NIEHS representatives were also panelists in a moderated discussion of issues related to endocrine disrupting chemicals (EDCs).

Understanding diseases with an environmental component

Birnbaum opened her talk by presenting her comprehensive definition of environment and placing endocrine disruption in the larger context of diseases with a known or suspected environmental component. She explained that environment is an important part of the matrix of disease causation, and emphasized the importance of indirect or delayed effects of exposure in shaping the endocrine signals that govern every organ and process in the body, as well as the frank manifestation of physiological harm, which classic toxicology calls apical endpoints.

“The main point here is that death or cancer are not the only endpoints that are important when considering environmental health,” she explained. “Reproductive function, brain development, lung function, and other physiological properties rely on proper development in order to maintain health, and environmental stressors can affect each of these functions.”

The presentation featured several detailed slides, including a schematic of the effects of insulin in tissue, underscoring the complexity and vulnerability of the endocrine system to EDC exposure in its many points of regulation and control. Birnbaum explained that EDCs are ubiquitous in the environment, occurring in a host of widely used pesticides and industrial chemicals. They can have a wide range of effects on health at low doses, especially when exposure occurs during windows of susceptibility in the course of development, she said.

Looking ahead, Birnbaum described the potential of Tox21, and other high-throughput, screening-based predictive toxicology efforts, in more comprehensively identifying potential EDCs and discovering new, relevant endocrine endpoints. She called for more research into mixtures, a sharper focus on public health, and the development of effective regulatory policy to help prevent disease.

Re-thinking dose response with EDCs

While Birnbaum's talk had been a survey of EDCs, Heindel's presentation focused on the characteristics and principles that convince him EDCs should be assessed according to different criteria than are used with most toxic substances. The basis of his argument was that the endocrine system functions according to distinct principles, and that, by implication, EDCs should be assessed according to six endocrine-specific principles:



Birnbaum was the only head of an American environmental health research organization at the workshop, although the U.S. Environmental Protection Agency and The Endocrine Society had representatives in attendance. (Photo courtesy of Steve McCaw)

- Hormones control everything in the human body, with multiple target tissues and organs, as distant from each other as the hypothalamus and the skeletal muscle in the lower extremities.
- Hormones act through tissue-specific receptors that can become saturated as doses increase.
- Hormones act at very low doses, as small as a few parts per trillion.
- Hormones regulate their own receptors, making the dose response more complex than it is with other toxic substances, because of the potential for saturating receptors.
- Due to overlapping pathways, hormones produce a non-typical dose-response curve, known as monotonic, which allows for decreases in the effect at some doses and increases at others.
- Hormonal action is life-stage specific, with tissue- and time-specific effects that are most harmful during development, leading to increased disease risk later in life.

Heindel closed by posing the question he anticipates will drive discussion in future efforts to better understand endocrine toxicology, “Are there sufficient data to incorporate low dose and non-monotonic responses and new endocrine endpoints into risk assessment?”

An upcoming [workshop](#) Sept. 11-13 in Berlin, co-sponsored by NIEHS, will address that very issue, with an assessment of low-dose data and data needs for defining a path forward.

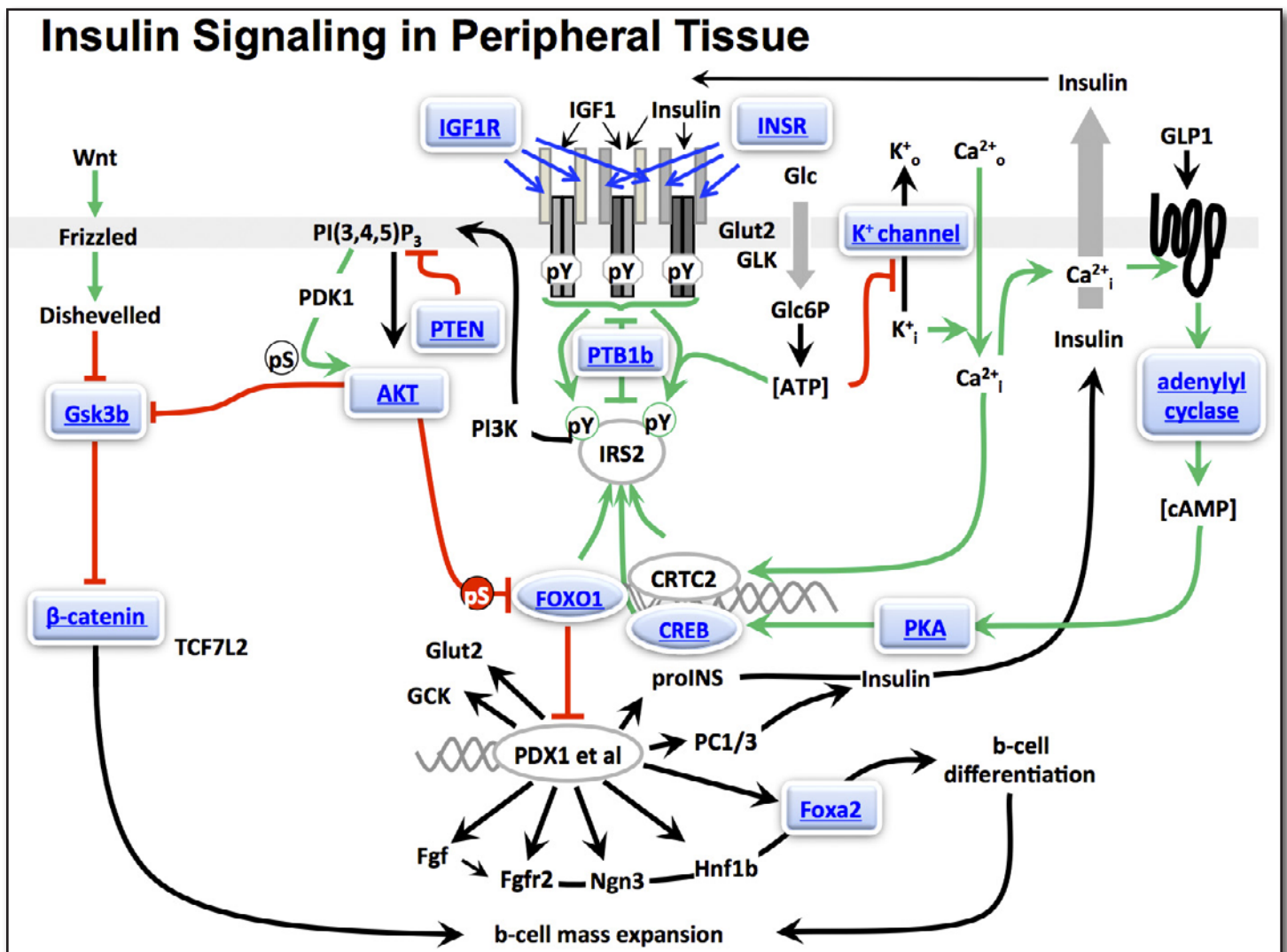


As part of his duties at NIEHS, Heindel oversees a portfolio of grants supporting research into the health effects of endocrine-disrupting chemicals. (Photo courtesy of Steve McCaw)

Moving forward with the EU community strategy for endocrine disruptors

Presentations and discussions at the conference explored the effects of endocrine disruptors on human health and the environment, the risks, the identification of endocrine disruptors, and policy objectives. Along with a report commissioned by the Directorate-General for the Environment in 2009 and published this year, [“State of the Art of the Assessment of Endocrine Disruptors,”](#) the outcome of the conference will feed into the review of the European Commission’s current strategy on endocrine disruptors. It will also provide input to the Commission’s upcoming proposal for criteria for the identification of substances with endocrine disrupting properties.

The EU [“Community Strategy for Endocrine Disruptors,”](#) first published in 1999, focused on short, medium, and long-term actions that, when implemented, would contribute to ensuring a better environment and health for people within the EU. The European Commission has supplemented the original strategy document with a series of implementation documents refining proposed actions.



Birnbaum used this schematic to emphasize the complexity of hormone signaling in peripheral tissues. “You can obviously see that there are many, many points of regulation and control in this system,” she said. (Image courtesy of Morris White, Ph.D.)

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Prenatal chlorpyrifos exposure alters brain structure, affects IQ in children

By Carol Kelly

A new NIEHS-funded [study](#) reports that when a pregnant woman is exposed to chlorpyrifos, a commonly used pesticide, her child’s developing brain may be damaged, leading to lowered intelligence.

“The prenatal period is a vulnerable time for the developing child, and that toxic exposure during this critical period can have far-reaching effects on brain development and behavioral functioning,” said NIEHS grantee [Virginia Rauh, Sc.D.](#), a professor at the Columbia University Mailman School of Public Health. “We have demonstrated that there is a relatively monotonic dose-response effect, suggesting that some small effects occur at even very low exposures.”

The evidence comes from researchers who conducted a recent brain imaging study of children exposed prenatally to chlorpyrifos. In addition to Columbia University scientists, the team included researchers affiliated with Duke University Medical Center, Emory University, and the New York State Psychiatric Institute.

This study is the first of its kind to use magnetic resonance imaging (MRI). Digital images produced from MRI scans are quite detailed and can detect small changes within the brain.

In the scans, structural changes — abnormal areas of enlargement and indentation across the surface of the brain — appeared among the children whose mothers had been exposed to higher levels of the pesticide. In three of four brain regions, higher chlorpyrifos exposure was consistent with lower full-scale intelligence quotient (IQ) measures in the exposed children.

The brain abnormalities appeared to occur at exposure levels below the current U.S. Environmental Protection Agency threshold for toxicity, according to the researchers.

Data implications

To conduct the study, certain brain surface features of 40 urban children were examined. The sample size, although modest, nevertheless permits generalization of findings to a larger urban population, because it was a representative community-based sample.

“The group does not have exposure to polycyclic aromatic hydrocarbons [PAHs] or second hand smoke, two other exposures that might also have adverse effects on brain development and neurocognitive outcomes,” explained Rauh. “So, the small sample size, common in MRI studies, is balanced by a relatively pure or unconfounded design.”

Although residential application of chlorpyrifos was banned in 2001, the insecticide is still approved for other uses. Chlorpyrifos continues to be present in the environment through its extensive use in wood treatments and public spaces, such as golf courses, parks, and highway medians. People near these sources can be exposed by inhaling the chemical, which drifts on the wind. Additionally, chlorpyrifos is approved for food agriculture, and exposure can also occur by eating fruits and vegetables that have been sprayed.

“Even if dietary doses from residue on food are low, and we think they are for any one food, what happens if a person is eating five different foods on a daily basis, each with a small amount of chlorpyrifos residue?” posited Rauh. “This is something to think about.”

Future research to continue examining pesticide effects on children

“It will be important to continue to follow this cohort of children, to see if the problems resolve or whether they are irreversible, which is an outcome suggested by animal research literature,” said Rauh. “It might be possible to design an intervention to address the moderate cognitive deficits.”

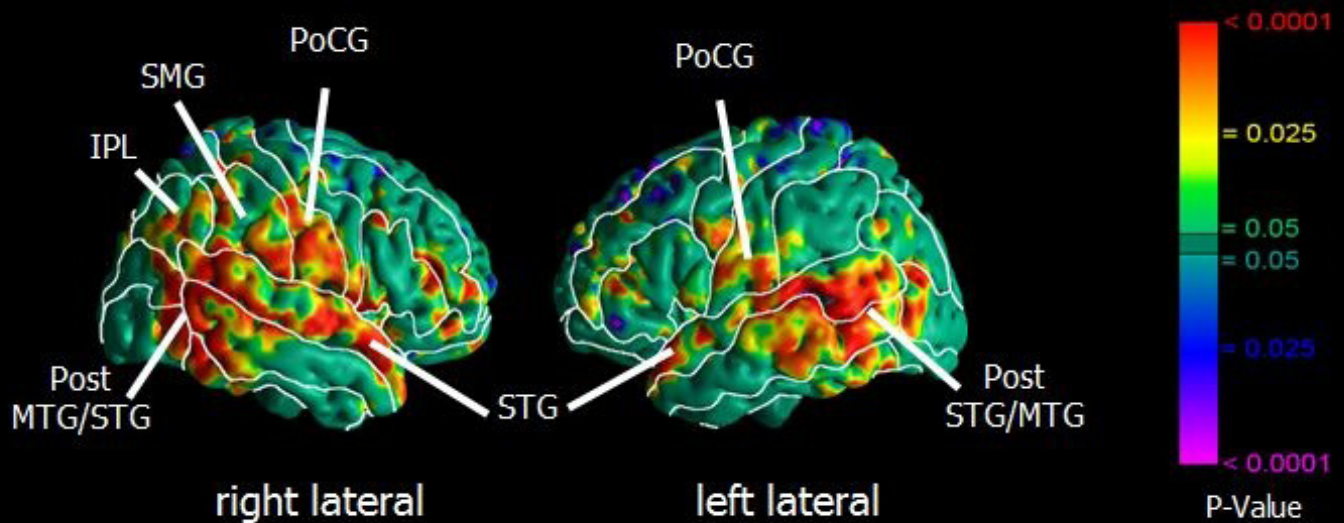
“If the animal studies suggest there may be a problem, and we follow up with human work that is confirmatory, then we would be wise to limit the use of such chemicals when the evidence starts to build up,” added Rauh. “There are plenty of examples of widespread or commonly used exposures, for example, lead and tobacco, where we waited too long to try to reduce exposure, with the unfortunate result of great harm to large numbers of individuals, which might have been preventable had we paid attention to the mounting evidence.”

This research was supported by NIEHS grants for [The Columbia Center for Children’s Environmental Health, Prenatal PAH Exposure, Epigenetic Changes, and Asthma](#), and [Health Effects of Early-Life Exposure to Urban Pollutants in Minority Children](#).



Rauh is deputy director of the CCCEH, which receives grant funding from the NIEHS and EPA. (Photo courtesy of Columbia University)

Effects of Chlorpyrifos Exposure on Brain Surface Measures



In these composite brain scan images, the warm colors (red to yellow) indicate enlargement of underlying white matter and cool colors (blue and purple) indicate indentation deformation. Areas of enlargement and deformation that relate to attention, receptive language, social cognition, and reward, emotion, and inhibitory control include the postcentral gyrus (PoCG), supramarginal gyrus (SMG), superior temporal gyrus (STG), inferior parietal lobe (IPL), and middle temporal gyrus (MTG). Significant abnormalities are associated with high chlorpyrifos exposure. (Image courtesy of Columbia University)

Building on previous findings

Previous work conducted at the Columbia Center for Children's Environmental Health (CCCEH) demonstrated exposure to pesticides during pregnancy harms the healthy growth and development of babies in the womb, as well as adversely affecting development in early childhood. Their studies are the first to follow exposed mothers and their offspring over time while documenting changes in the children's cognitive development.

A 2006 CCCEH study showed that children who were prenatally exposed to chlorpyrifos had significantly worse cognitive and motor development at age 3. Early delays affect children's ability to learn and their later school performance. These children were also significantly more likely to score in the clinical range for behavioral and attention problems such as attention deficit hyperactivity disorder, a condition associated with altered brain functioning and characterized by an inability to focus on tasks.

"These findings indicate that prenatal exposure to the insecticide chlorpyrifos not only increases the likelihood of developmental delay, but may have long-term consequences for social adjustment and academic achievement," said Rauh, in a Columbia press release about the 2006 study.

In a 2011 CCCEH study involving urban minority mothers, children born to women who had the highest levels of chlorpyrifos in their cord blood during delivery scored three points lower on IQ tests at age 7, compared with children born to mothers with the lowest levels of the pesticide. The relationship persisted even after accounting for other factors that could explain differences in IQ, such as maternal education, the home environment, and possible underlying attention or development disorders.

Citation: [Rauh VA, Perera FP, Horton MK, Whyatt RM, Bansal R, Hao X, Liu J, Barr DB, Slotkin TA, Peterson BS. 2012. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. Proc Natl Acad Sci 109\(20\):7871-7876.](#)

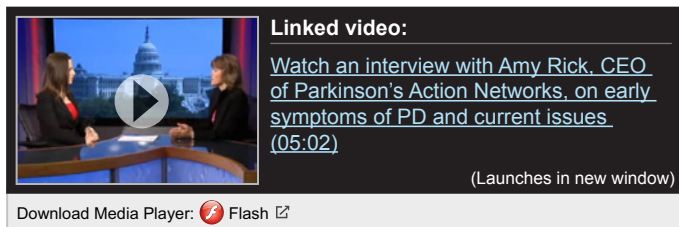
(Carol Kelly is a research and communication specialist with MDB, Inc., a contractor for the NIEHS Division of Extramural Research and Training.)

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Connecting the dots in Parkinson's disease

By Ernie Hood

The first image that comes to mind about Parkinson's disease (PD) is likely to be the classic muscular tremors associated with famous patients such as Michael J. Fox and Muhammad Ali. But the condition actually begins to manifest itself much earlier than the onset of those motor symptoms, with a variety of nonmotor or premotor symptoms that may appear decades prior to the motor features. Scientific understanding of the role of premotor symptoms in the etiology, development, and progression of PD is at an early stage, but the existing research is intriguing and the potential for important new knowledge to emerge is enormous.



The potential is what led approximately twenty leading experts in the field to gather June 7-8 at the Parkinson's Disease Premotor Symptom Symposium. The meeting was co-organized by NIEHS epidemiologist [Honglei Chen, M.D., Ph.D.](#), and program administrator [Cindy Lawler, Ph.D.](#) "We were interested in organizing this symposium because, first, by studying the premotor symptoms, we may get a window to identify the disease early, and equally important, we may learn more about early disease etiology," said Chen.

"We need to be looking more broadly at Parkinson's disease as a systemic illness," explained Lawler. "There has been a focus on the motor symptoms and the dopamine system in the substantia nigra, effects that occur later in the disease process. If we really want to have a chance to alter the progression of the disease, we need to look earlier at this broader constellation of signs and symptoms that are very important in terms of quality of life and, at least in some cases, appear to precede the onset of motor symptoms."



According to Chen, at least one million Americans currently have PD, with an annual cost of \$25 billion. "If we identify a potential combination of premotor symptoms that is highly predictive of the disease, we can study the environmental factors that are related to either disease development or disease progression," Chen told participants. (Photo courtesy of Steve McCaw)

According to research findings presented at the symposium, that broader constellation of signs and symptoms includes constipation, loss of sense of smell, excessive daytime sleepiness, and mood or anxiety disorders, as well as REM sleep behavior disorder, characterized by kicking or other jerky movements during deep sleep. Some of the conditions, particularly in combination, can be quite debilitating and may appear up to twenty years prior to the development of the classic motor symptoms.

Three areas of research

The symposium devoted three main sessions to the topics of clinical research and epidemiology; animal models and mechanisms; and neuroimaging, pathology, and biomarkers. As the meeting progressed, it was clear the researchers were excited by what they were learning from their colleagues and eager to pursue new types of collaborations to explore the role of PD premotor symptoms.

Although the findings are tantalizing, the speakers agreed that none of the symptoms by themselves are specific or sensitive enough to be definitively considered predictive precursors to PD. Identifying combinations of premotor symptoms that would be reliably predictive would enable earlier detection and intervention, with a goal of halting or at least slowing progression of the disease.

“Because there is such a long preclinical phase of Parkinson’s, when people have some nonmotor symptoms, but have not developed motor symptoms, that would be the time to intervene with neuroprotective strategies,” said Lawler. “If you could find a way to even keep them at that level of functioning, it would have a tremendous impact on quality of life.”

New directions

Addressing the gaps in the research will be very challenging, but the opportunity to elucidate PD etiology and enhance prevention or provide clinical treatment, will encourage researchers to continue to analyze premotor symptoms, incorporating some of the new ideas they heard at the meeting. The results of the meeting will be used to help define high priority areas for future extramural investments in NIEHS Parkinson’s disease research, said Lawler. “This is going to take a lot of effort in thinking of, and planning for, the best strategy to work on the premotor symptoms,” said Chen. “The symposium gave me a lot of ideas about which premotor symptoms I should focus on, what kind of planning work I need to think about, and what are the important questions I need to address.”

(Ernie Hood is a contract writer for the NIEHS Office of Communications and Public Liaison.)



“This is kind of a new field of research,” said NIEHS/NTP Director Linda Birnbaum, Ph.D., as she welcomed participants to the symposium. “It’s really just evolving, and we’re happy to have this minisymposium to lay out the research priorities and strategies that need to be looked at.” (Photo courtesy of Steve McCaw)



Discussions among the investigators in attendance were lively and enthusiastic. Rodolfo Savica, M.D., presented findings from Mayo Clinic research on PD premotor symptoms, using electronic databases to tease out possible associations and timelines. (Photo courtesy of Steve McCaw)

The dual-hit hypothesis

Growing interest in exploring how premotor research can improve our understanding on PD etiology, at least partially, arises from the hypothesis put forward in 2003 by German anatomist Heiko Braak, M.D., and colleagues. Braak and the others expanded on the hypothesis in a 2007 paper titled “Parkinson’s disease: a dual-hit hypothesis,” in which the researchers posit a viral PD etiology, with the virus entering different regions of the brain from both the gut and the olfactory bulb. The publication’s abstract outlines the concept.

Accumulating evidence suggests that sporadic Parkinson’s disease has a long prodromal period during which several non-motor features develop, in particular, impairment of olfaction, vagal dysfunction and sleep disorder. Early sites of Lewy pathology are the olfactory bulb and enteric plexus of the stomach. We propose that a neurotropic pathogen, probably viral, enters the brain via two routes: (i) nasal, with anterograde progression into the temporal lobe; and (ii) gastric, secondary to swallowing of nasal secretions in saliva. These secretions might contain a neurotropic pathogen that, after penetration of the epithelial lining, could enter axons of the Meissner’s plexus and, via transsynaptic transmission, reach the preganglionic parasympathetic motor neurones of the vagus nerve. This would allow retrograde transport into the medulla and, from here, into the pons and midbrain until the substantia nigra is reached and typical aspects of disease commence. Evidence for this theory from the perspective of olfactory and autonomic dysfunction is reviewed, and the possible routes of pathogenic invasion are considered. It is concluded that the most parsimonious explanation for the initial events of sporadic Parkinson’s disease is pathogenic access to the brain through the stomach and nose — hence the term ‘dual-hit.’

Citations:

Braak H, Rüb U, Gai WP, Del Tredici K. 2003. Idiopathic Parkinson’s disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm* 110(5):517-536.

Hawkes CH, Del Tredici K, Braak H. 2007. Parkinson’s disease: a dual-hit hypothesis. *Neuropathol Appl Neurobiol* 33(6):599-614.



Lawler moderated the second of the meeting’s three sessions, which was devoted to animal models and mechanisms. She noted that NIEHS would encourage researchers to submit applications that focus on PD premotor symptoms, an area currently under-represented in the Institute’s research portfolio. (Photo courtesy of Steve McCaw)



Amy Rick, of the Parkinson’s Action Networks, represented the patient advocacy community at the symposium. “What you learn is also hugely relevant to the current generation of people with Parkinson’s... [to] help people who now have these nonmotor symptoms that are incredibly disruptive.” (Photo courtesy of Steve McCaw)



G. Webster Ross, M.D., presented findings from the Honolulu-Asia Aging Study cohort. His team of researchers found a three-fold risk for PD among people with constipation. Premotor symptoms, he said, appeared as early as 24 years before clinical diagnosis. (Photo courtesy of Steve McCaw)



NIEHS researcher Jau-Shyong Hong, Ph.D., who is head of the NIEHS Neuropharmacology Group, spoke on "Inflammation-mediated neurodegenerative animal models for studying mechanisms and therapy of Parkinson's disease." (Photo courtesy of Steve McCaw)



Shown left to right, researchers Robert Nussbaum, M.D., of the University of California, San Francisco; Jing Zhang, M.D., Ph.D., of the University of Washington; and Alberto Ascherio, M.D., Dr. P.H., of the Harvard School of Public Health, were among the presenters at the symposium. (Photo courtesy of Steve McCaw)



To commemorate the occasion, symposium organizers and attendees gathered on the NIEHS patio for a group portrait. (Photo courtesy of Steve McCaw)

Transcription factor binding dominates talks at minisymposium

By Jeffrey Stumpf

A cast of scientists at the forefront of 21st century techniques was on hand at NIEHS May 29-30 for a pair of half-day symposia. NIEHS researcher [Leping Li, Ph.D.](#), organized the nine talks on motif discovery and sequence data analysis that attracted renowned scientists from prestigious universities, as well as an NIEHS audience with wide-ranging interests. Li's colleagues [Pierre Bushel, Ph.D.](#), of NIEHS, and [Jason Lieb, Ph.D.](#), of the University of North Carolina at Chapel Hill, chaired the sessions.

Duke University researcher [Greg Crawford, Ph.D.](#), summarized the speakers' interests in genome sciences by reminding the audience that 98 percent of the genome does not code for amino acid sequences. The meeting emphasized many ways that the noncoding regions are involved in gene regulation.

Recurring motifs describe nucleotide binding

Transcription factors bind to DNA at consensus sequences, or motifs, to regulate gene expression. Keynote speaker [Gary Stormo, Ph.D.](#), from Washington University in St. Louis, provided a multidisciplinary approach to understanding where transcription factors bind. Stormo used high-throughput experiments to measure the short DNA sequences to which transcription factors bind and promote changes in expression. These methods would ultimately be used to determine binding site motifs based on the amino acid sequence of the protein.

While DNA was the favored nucleotide at the symposium, Brown University computational biologist, [Charles Lawrence, Ph.D.](#), proudly provided a respite. "I promise, there will be no DNA in this talk," joked Lawrence, who instead focused on gene regulation by microRNAs (miRNAs). An average of only 22 nucleotides long, miRNAs are prevalent in the human genome and repress gene expression by binding to transcripts. Because finding the target for miRNAs is difficult, Lawrence discussed how his mathematical models not only improve prediction of miRNA secondary structures, but also dissect a possible transcript-binding motif.



Li welcomed speakers from across the nation to NIEHS. In addition to organizing the meeting, Li presented his research on characterizing binding sites of the transcriptional repressor CTCF. (Photo courtesy of Michael Garske)



A captive audience studied the complex statistical formulas presented by Stormo during his keynote address. Referring to a slide showing rows of hundreds of colorful DNA motifs, Stormo suggested that he should "sell it as wall paper." (Photo courtesy of Michael Garske)

When the nucleosomes are away, the transcription factors play

Although DNA binding motifs are useful in discovering transcriptional networks, there are determinants for DNA binding other than sequence. In the course of a session that showcased how researchers took advantage of locating regions where nucleosomes bind DNA, several speakers emphasized that the binding of nucleosomes to DNA deters transcription factor activation.

“We can use nucleosome eviction as a marker to predict interesting regulatory activity,” Lieb explained.

Cliff Meyer, Ph.D., a researcher at the Harvard School of Public Health, likened the study of transcription factor binding to Plato’s famous example of inferring truth from shadows in his Allegory of the Cave. To ascend from the proverbial cave, Meyer identified regions that are hypersensitive to DNase treatment, indicating sections of the genome where nucleosomes bind less frequently.

“The upregulation of gene expression correlated with the lack of nucleosome occupancy globally and vice versa,” Meyer explained.

Lieb used a similar approach to determine nucleosome occupancy but applied it to *Drosophila* development. By searching regions with decreased nucleosome binding, Lieb identified a regulatory element in a 27-kilobase region that programs cells to become halteres, structures that improve balance during *Drosophila* flight. Furthermore, Lieb described chromatin profiles of various cell fates at different times, and was surprised by the conclusion.

“Regarding the chromatin profile, different tissues at the same stage in development are more similar than their own daughter cells,” Lieb summarized.

Computer modeling aims for usefulness

In light of the biological data presented by Lieb and Meyer, Duke University professor **Alexander Hartemink, Ph.D.**, provided a computer-generated model called COMPETE to visualize the competition between nucleosomes and transcription factors in binding DNA. His model demonstrated that increasing one transcription factor might displace nucleosomes to other regions, causing reduced binding of nearby transcription factors.

Considering his model was developed using only computational methods, Hartemink interpreted his results cautiously, reminding the audience of a quote from the statistician George Box, Ph.D., “All models are wrong, but some models are useful.”



Liu, a Harvard professor, addressed Li’s question about his work on the local, three-dimensional structure of DNA. Liu noted his improvements on current methods. “Their analysis takes weeks – ours takes seconds,” Liu announced. (Photo courtesy of Michael Garske)



Bushel, left, a staff scientist in the biostatistics branch, moderated questions addressed to Meyer after his talk. Bushel chaired the first session of the symposium. (Photo courtesy of Michael Garske)



Hartemink explained how he arrived at the computer model that displayed what he called an ensemble view of promoter occupancy. (Photo courtesy of Michael Garske)



Lieb spoke about how the presence or absence of nucleosomes can affect whether genes are turned on or off. Nucleosome occupancy, Lieb proposes, is one of many ways that describe how cells differentiate. "We start as one cell with one genome and turn into an exquisite trillion cell organism." (Photo courtesy of Michael Garske)



Lawrence, left, enjoyed talking to Li during a break immediately before his lecture. In addition to modeling RNA secondary structure, Lawrence discussed how he has found uses for his mathematical prowess in paleobiology. (Photo courtesy of Michael Garske)



Ernst, a UCLA professor, discussed chromatin modification and transcription factor binding. In introducing Ernst, Lieb noted the complexity of his topic. "Histone tails can have dizzying arrays of modifications," Lieb warned. (Photo courtesy of Michael Garske)

Symposium highlights cross talk between biologists and computer scientists

The search for DNA binding motifs involves high-throughput techniques that only have been possible within the last decade. NIEHS Scientific Director Darryl Zeldin, M.D., introduced the symposium with the message that mining through the wealth of data is our next greatest challenge.

“As our ability to generate large amounts of genetic data has advanced at an astronomical rate, our ability to analyze the data and understand fundamental biological questions has not [advanced at the same pace],” Zeldin remarked.

Li also acknowledged the importance of mixing the best of two separate, yet equally, important worlds.

“Advances in technologies such as next-gen sequencing make it possible to study genome-wide gene expression or protein binding in a single experiment,” Li noted. “However, making sense of the huge amount of data remains a challenge, making bioinformatics an increasingly integral part of modern biology.”

The marriage of two distinct disciplines not only has shaped today’s research, but also has provided the science community with many computational tools. Many of these programs are publicly available, including ENCODE (the Encyclopedia of DNA Elements, produced by Crawford), BACH (Bayesian 3D constructor for Hi-C data, described by speaker [Jun Liu, Ph.D.](#), of the Harvard School of Public Health), ChromHMM (Chromatin-state discovery and characterization, written by speaker [Jason Ernst, Ph.D.](#), of UCLA), and COMPETE.

Although the symposium featured speakers with diverse experience and expertise, Zeldin noted their common attributes.

“These are internationally recognized thought leaders who have achieved both successes — not only dealing with sophisticated biological questions, but also rendering the findings accessible to answer important environmental health problems,” Zeldin concluded.

(Jeffrey Stumpf, Ph.D., is a research fellow in the NIEHS Laboratory of Molecular Genetics Mitochondrial DNA Replication Group and a regular contributor to the Environmental Factor.)

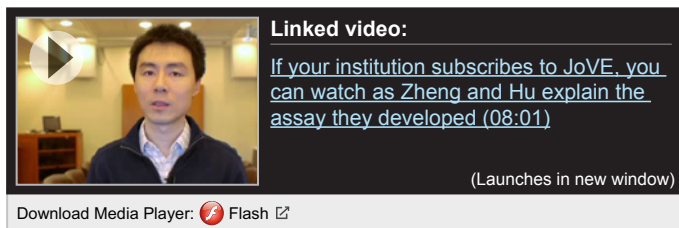
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NIEHS researchers publish in scientific video journal

By Robin Arnette

For researchers, being able to duplicate the results that appear in journal articles is fundamental to science, but even the most meticulously written materials and methods section doesn’t explain all of the essential details. That’s why Laboratory of Molecular Carcinogenesis (LMC) researcher [Guang Hu, Ph.D.](#), and visiting fellow Xiaofeng Zheng, Ph.D., used a video to demonstrate the procedures they used in their experiments.

Zheng and Hu published their findings in the [Journal of Visualized Experiments \(JoVE\)](#), the first scientific journal dedicated to capturing the intricacies of life science research using printed word and video. Their [paper](#), titled “Oct4GiP reporter assay to study genes that regulate mouse embryonic stem cell maintenance and self-renewal,” appeared online May 30 in JoVE.



Lights, camera, action

A JoVE videographer came to NIEHS and filmed Zheng doing a technique he and Hu developed called the Oct4GiP reporter assay. The assay allows researchers to quickly identify and study important genes in mouse embryonic stem cell self-renewal and differentiation.

“Compared to other methods, it is more convenient, sensitive, quantitative, and has a lower cost,” Zheng said of the procedure. “It is especially suited for large-scale studies such as high-throughput screens or genetic epistasis analysis.”

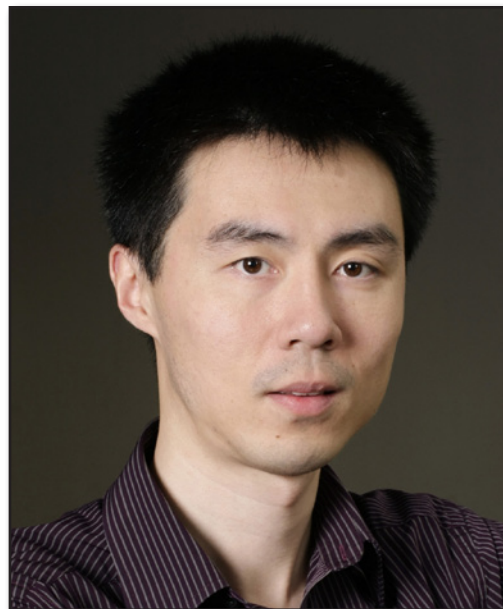
One of the steps of the Oct4GiP reporter assay requires introducing small interfering RNAs (siRNAs) artificially into cells, also known as transfection. Zheng had to carefully calculate, count, pipet, and mix the transfection reagents and cells to ensure that the cells were evenly plated and that a majority of them successfully received the siRNAs. Zheng and Hu believe having the step-by-step process on video will help other scientists bypass many of the potential pitfalls that could lead to experimental failure.

Seeing is believing

JoVE started in 2006 and, since June 2012, has published 64 issues containing more than 1,700 video protocols. The videos are divided into six categories: general, neuroscience, immunology and infection, clinical and translational medicine, bioengineering, and applied physics.

Although Zheng and Hu are the first NIEHS investigators to publish in JoVE, 12 other institutes within the National Institutes of Health have released JoVE video articles. Several local universities have gotten in on the action, as well. Duke University leads the way with 15 JoVE videos. The University of North Carolina at Chapel Hill has seven, while North Carolina State University has two. North Carolina Central University rounds out the list with one.

Hu said that he and his group found out about JoVE a few years ago, and benefitted from watching several of their video protocols. When it came time to publish their work on the Oct4GiP reporter assay, they didn’t hesitate to submit their manuscript to JoVE.



Hu leads the Stem Cell Biology Group within LMC. His group studies the molecular basis of self-renewal and differentiation in embryonic stem cells. (Photo courtesy of Steve McCaw)



Zheng is prominently featured in the JoVE video. (Photo courtesy of Steve McCaw)

“Presenting the assay in a video format provides visual guidance for people who are not familiar with the techniques,” Hu said. “It helps them perform the experiments much more easily and is more effective than just reading the text.”

Citation: Zheng X, Hu G. 2012. Oct4GiP reporter assay to study genes that regulate mouse embryonic stem cell maintenance and self-renewal. J Vis Exp 63:e3987; doi:10.3791/3987 [Online 30 May 2012].

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Pollution and obesity impact asthma control in seniors

By Eddy Ball

A new [study](#), funded in part by NIEHS, explores the effects of traffic pollution and obesity on the growing number of asthmatics in the U.S. who are 65 or older. The paper appears in the June issue of the *Annals of Allergy, Asthma, and Immunology*.

Despite the public health implications of the high rates of morbidity and nearly five-times greater asthma-related mortality in this population, the researchers wrote, predictors of asthma control in older people remain poorly understood. To the researchers’ knowledge, theirs is the first study to demonstrate a significant association between estimated daily residential exposure to diesel particulate matter and asthma severity in people 65 and older, who make up two-thirds of asthma-related deaths each year.

“Poor asthma control can lead to a decreased quality of life and an increased risk for emergency department visits, hospitalizations, and death,” lead author [Tolly Epstein, M.D.](#), was quoted as saying in a University of Cincinnati (UC) [press release](#). Epstein is an assistant professor in the division of immunology, allergy, and rheumatology in UC’s Department of Internal Medicine and a UC Health allergist who headed the team of eight clinicians and environmental scientists.



Lead author Tolly Epstein worked with colleagues from UC, the Cincinnati Veterans Administration Medical Center, and the Bernstein Clinical Research Center. (Photo courtesy of UC)

A growing public health issue

“The health effect of outdoor air pollutants on asthma in baby boomers, as well as young children, is substantial and underappreciated,” said study co-author David Bernstein, M.D., a professor in the UC immunology, allergy, and rheumatology division and also a UC Health allergist.

According to the study’s authors, this population, with an asthma prevalence rate as high as ten percent, is estimated currently to include 3.1 million people and is expected to double within the next 25 years. Seniors typically experience higher rates of obesity as well, which the study found was also associated with poorer asthma control. In addition, obesity may have exacerbated host responses to traffic pollution for people with asthma. Reasons for this are unclear, but could possibly be due to weight-related inflammation. The researchers speculated that an age-related decline in antioxidant defenses may explain why older asthmatics are especially susceptible to the effects of such air pollutants as nitrogen dioxide, ozone, and fine particulate matter.

Asthmatic seniors in Cincinnati

The researchers, all of whom have experience with similar studies involving children, carefully controlled the selection and study of their population of 104 patients, 65 years or older, who were recruited from allergy and clinical programs in the greater Cincinnati area. Enrollment required a physician's diagnosis of asthma as well as independent clinical confirmation based on objective testing. The team excluded patients with chronic obstructive pulmonary disease or congestive heart failure.

The participants completed a standardized, close-ended demographics and medical questionnaire, which was verified with medical records, and the Asthma Control Questionnaire (ACQ), which was used to quantify symptom severity. The team estimated daily exposure to elemental carbon attributable to traffic (ECAT) using a land-use regression model based on the participant's current residential address.

Analysis showed that participants exposed to higher levels of ECAT were nearly three times more likely to have higher ACQ scores, indicating more severe symptoms. Obese participants, defined as those with a body mass index greater than 30, were more than five times as likely to have higher ACQ scores.

NIEHS support

The NIEHS-funded UC [Center for Environmental Genetics](#) and a U.S. Public Health Service grant provided support for the study. The university's NIH-funded [Center for Clinical and Translational Science and Training](#) made a Mentored Clinical Scientist Development Program Award to Epstein for this research.

Citation: [Epstein TG, Ryan PH, LeMasters GK, Bernstein CK, Levin LS, Bernstein JA, Villareal MS, Bernstein DI](#). 2012. Poor asthma control and exposure to traffic pollutants and obesity in older adults. *Ann Allergy Asthma Immunol* 108(6):423-428.

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Senior author David Bernstein is a fellow of the American College of Allergy, Asthma, and Immunology and a principal in the [Bernstein Clinical Research Center](#). (Photo courtesy of UC)

Study links house dust with high risk of exposure to flame retardant chemicals

By Ashley Godfrey

In a new NIEHS-funded study of polybrominated diphenyl ethers (PBDEs), chemicals used as flame retardants, NIEHS Outstanding New Environmental Scientist (ONES) awardee [Heather Stapleton, Ph.D.](#), and colleagues found that toddlers have a significant amount of exposure to PDBEs through house dust.

The [findings](#), published online in *Environmental Health Perspectives*, suggest that hand-to-mouth activity may be a significant source of exposure for children 12 to 36 months of age. Children's exposure to these chemicals is a concern, because many studies, both in animals and humans, have shown that PBDEs have potential

endocrine disrupting effects and may have harmful effects when exposures occur during critical periods of neurodevelopment. PBDEs have chemical structures similar to thyroid hormones.

According to Stapleton, indoor dust levels of PBDEs are higher than most people would expect, and are surprisingly similar to the levels she and her colleagues found in a related study that measured PBDEs in municipal sewage sludge.

From house dust to hands

One of the primary objectives of this study was to better characterize children's exposure to PBDEs from house dust, while also examining the relationship between PBDE exposure and other variables that may affect exposure. The study enrolled 83 children in North Carolina and measured PBDE levels in blood and hand wipe samples taken from each child, as well as in house dust samples. The researchers found a strong correlation between the PBDE levels found on the hand wipes and the levels measured in the blood.

The findings suggest that toddlers have a significant amount of exposure to PBDEs by transferring house dust particles from their hands to their mouths. This suggests exposure to other household dust contaminants, such as pesticides, polycyclic aromatic hydrocarbons (PAHs), perfluorinated compounds (PFCs), and other types of flame retardants, may occur the same way. PAHs are produced as byproducts of burning fuel, while PFCs are found in products that resist stains, oil, and water. All of these contaminants are believed to pose a human health risk.

The methods used in this study also suggest the value of using hand wipes as a tool to measure children's exposure to different chemicals found in dust. "Hand wipes might be a better route to measure exposure," Stapleton said.

Other risk variables

The study also found other factors that may contribute to exposure levels, including age, socioeconomic status, and duration of breastfeeding. While these factors may be significant predictors of exposure levels, the study points out that further research is needed to explore why these factors are influencing PBDE exposure in children. This information may help in mediating the potential health risks from exposure, by increasing public awareness about what other factors contribute to exposure.

When asked about the importance of this line of research, Stapleton said the study is only one of many that she feels are necessary, in order to gather as much information as possible about children's exposure to PBDEs and other chemicals found in dust, to understand the potential health risks that may come from this type of exposure.

Public health concerns

Although two forms of PBDEs, pentaBDE and octaBDE, were phased out of use in the U.S. in 2004, and a third, decaBDE, is scheduled to be voluntarily phased out starting in 2013, it is impossible to determine



Stapleton, an assistant professor of environmental chemistry at the Duke University Nicholas School of the Environment, feels very strongly about the potential health risks of PBDE exposure in young children and is doing everything she can to help spread public awareness. Stapleton spent the early part of her career working under the guidance of NIEHS/ NTP Director Linda Birnbaum, Ph.D., who is recognized as a leading authority on flame retardant research. (Photo courtesy of Duke University Nicholas School of the Environment)

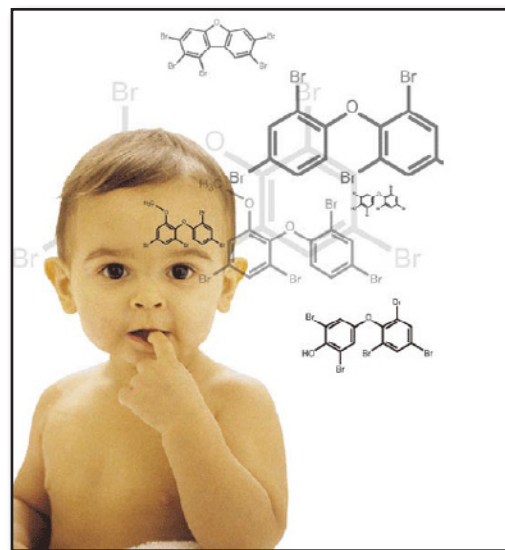
exactly which household products are treated with these chemicals. Many PBDEs are known to have very long half-lives, the period of time it takes for the amount of a substance undergoing decay to decrease by half, and can potentially still find their way into house dust from older products in the home.

Stapleton is also interested in conducting future studies to investigate exposure from new flame retardants that are now on the market and are being used to replace the phased-out PBDEs. Children, as well as adults, are more likely to be exposed to a complex mixture of chemicals, instead of just one, because there are so many chemicals found in house dust. “We know very little about the health effects from exposure to complex mixtures of chemicals,” acknowledged Stapleton.

Citation: Stapleton HM, Eagle S, Sjödin A, Webster TF. 2012. Serum PBDEs in a North Carolina toddler cohort: associations with hand wipes, house dust and socioeconomic variables. *Environ Health Perspect*; doi:10.1289/ehp.1104802 [Online 23 May 2012].

(Ashley Godfrey, Ph.D., is a postdoctoral fellow in the Molecular and Genetic Epidemiology Group in the NIEHS Laboratory of Molecular Carcinogenesis.)

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Young children have very high hand-to-mouth activity and are, therefore, at increased risk of exposure to PBDEs through house dust. Stapleton suggested that regular handwashing, along with education and the practice of other clean behaviors, may help to lower the amount of exposure. (Photo courtesy of Environment California)

Confronting the issue of heritability in large-scale genetic studies

By Eddy Ball

In the first of two symposia in May on large-scale genetic studies, world-renowned experts tackled the genome-wide association studies (GWAS) dilemma — a proliferation of data that has frustrated scientists by thus far failing to fully realize the potential for better understanding disease risk and host response.

GWAS examine many common genetic variants in different individuals to see if any variant is associated with a trait. GWAS typically focus on associations between single nucleotide polymorphisms (SNPs) and traits such as major diseases. Sample sizes have grown progressively larger due to high-throughput screening capabilities, surveying millions of SNPs in recent studies.

Organized by NIEHS Biostatistics Branch lead researcher [Dmitri Zaykin, Ph.D.](#), and research fellow [Chia-Ling Kuo, Ph.D.](#), the symposium May 24-25



Woychik placed large-scale association studies within the context of personalized health. “It’s really about better understanding the genes, the variations of the genes, and the other factors that are responsible within you, as an individual, or me, for how we respond to complex mixtures and factors in our environment,” he explained. (Photo courtesy of Steve McCaw)

on “Emerging issues in analysis and design of large scale genetic studies” featured eight presentations on large-scale association studies, moderated by NIEHS epidemiologists [Jack Taylor, M.D., Ph.D.](#), and [Stephanie London, M.D., Dr.P.H.](#) Among the topics addressed were large-scale aspects of modern genetic studies, advances in identification of genuine signals, the problem of missing heritability, design of discovery and replication stages of studies, risk magnitude distribution in the genome, pathway analyses, and approaches for analysis of rare variants.

“It’s absolutely clear that this issue of differential host response to the environment is just pivotal to any of the goals associated with our strategic plan,” said NIEHS Deputy Director Rick Woychik, Ph.D., in welcoming remarks. “Why is it that, although we are all exposed to the same environment, there are different health consequences?”

Statistical approaches

In his keynote address, University of Washington biostatistician and geneticist [Bruce Weir, Ph.D.](#), discussed classic studies in the heritability of human height, beginning with the data and findings published in 1886 by Francis Galton. While family studies have demonstrated that 80 percent of height is heritable, search for genetic variants associated with height could not account for more than 10 percent. Weir presented recent advances in statistical methodology that increased that figure to 45 percent and discussed ways to account for the remaining 35 percent. Weir’s fellow presenter [Daniel Stram, Ph.D.](#), of the University of Southern California, as well as other speakers on the program, are striving to account for the complexity of heritability, by better capturing the strong polygenic signal created by additive heritability of many common variants.

A common theme among the statisticians at the meeting was the need for even larger sample sizes, for utilizing hidden heritability associated with common SNPs, by building statistical models that are more sensitive to hidden stratification, to unravel the genetic architecture involved. Speakers proposed several statistical refinements, such as variance components methods, ensemble or set testing that aggregates individual features, and a prototype similarity collapsing approach for more effectively capturing additive and non-additive effects among markers.

Biological approaches

As part of a symposium that was filled with statistical discussion, University of Chicago geneticist [Nancy Cox, Ph.D.](#), spoke on tying biological function to analyses, and North Carolina State University geneticist [Trudy Mackay, Ph.D.](#), addressed the genetic and environmental factors affecting variation in quantitative traits, using *Drosophila* as a model system.



Weir said of Galton’s work, “The numbers were wrong, but the idea was right.” Much larger numbers in more recent studies suggested as many as 135 SNPs are associated with height but, collectively, they accounted for only 10 percent of variation in height. (Photo courtesy of Steve McCaw)



The presenters, such as Stram, often disagreed about methodology, but they almost uniformly called for more data. “We need a lot of data to have some faith in the results,” Stram said. (Photo courtesy of Steve McCaw)

Cox's focus in her talk was on the role of transcriptional function in the effects of SNPs on disease and risk. "For me," she said, "it's more about function." Referring to results from her bipolar study, she explained that effects of SNPs may vary from tissue to tissue, depending on whether there is significant enrichment by cis-acting elements, DNA sequences in the vicinity of the structural portion of a gene that are required for gene expression, or by trans-acting factors that bind to cis-acting sequences to control gene expression.

For Mackay, there are insights to be gained from recapitulating known biological pathways in model organisms that retain the same function as they do for humans, as a large-scale association study general strategy test. Supported by NIEHS funding, Mackay mated *Drosophila*, randomly through more than 70 generations, to create diversity for studying differences in genetic architecture among gene networks and expanding the findings of a genome scan.

The challenges of large-scale association studies

As the symposium at NIEHS demonstrated, there are two major approaches to teasing more translatable information from the volumes of data available from large-scale association studies. One deductive approach is to refine analysis methodology to give associations between data and endpoints more statistical power. The second, more inductive in nature, involves grounding large-scale association study statistical analysis in biology itself, through analysis of function and orthological patterns with model species.

Both approaches seek to illuminate what has been described as the dark matter of the genome — missing heritability. Current statistical approaches are limited in that they account for only the additive part of heritability — the variation transmittable from parents to offspring. However, joint effects of allelic variants, while genetic, are not transmittable in the same way, because specific combinations of variants are broken down by recombination.

As Zaykin explained, the non-additive part can be substantial. There is also a problem of predicting individual risk. It is one question to explain genetic variation using a sample. It is another, and still unsolved, question of how to predict risk for an individual given his or her sequence data. The technological limitation is the still incomplete coverage of all variants of individual genomes.



According to Cox, diversity and functional variation are important to understanding disease and risk. "There is a tremendous array of very rare variants in human populations," she said. (Photo courtesy of Steve McCaw)



Mackay's group looked at a great range of complex traits, in flies, affecting the host response involved in chill coma recovery, startle response, and starvation resistance. "The same mutations have different effects in different genetic backgrounds," she explained. (Photo courtesy of Steve McCaw)

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Workshop on informed risk assessment ponders new directions

By Cindy Loose

Emerging scientific advances could transform the way scientists analyze the risk of toxic substances to humans, allowing both more efficient and more exact risk assessments.

“Making that leap, however, is harder than it sounds, and it sounds pretty hard,” said John Balbus, M.D., NIEHS senior advisor for public health. His remarks came during the opening of a two-day [workshop](#) June 14-15 sponsored by NIEHS. The workshop was the 11th workshop in the [Emerging Science for Environmental Health Decisions](#) series begun in 2009.

Scientists from around the world gathered for the meeting in a continuing attempt to bridge the gap between traditional toxicology assessment — testing of animals to examine one chemical at a time — and new techniques that research the complex actions of chemicals in the human organism using molecular and systems biology, toxicogenomics, computational toxicology, and other emerging sciences.

Confronting the backlog of untested chemicals

“This is the next step in a long, deliberate march,” said Balbus, describing the purpose of the Systems Biology — Informed Risk Assessment workshop held at the National Academy of Sciences in Washington, D.C. “There are a lot of chemicals out there that still need to be tested, and we’re trying to create a better system for public health protection.”

The vast majority of the more than 100,000 chemicals estimated to be in use have never been tested for toxicity and, each year, thousands of new man-made chemical compounds are created.

Keynote speaker [Kim Boekelheide, M.D., Ph.D.](#), a professor at Brown University and a veteran NIEHS grantee, warned that changing risk assessment by using new biology at the molecular level will require breaking the traditional framework that has been in place for 50 years. The current system, he said, is simplistic and linear, with the goal of setting one number as an exposure threshold.

A dynamic, interactive model for toxicology

Systems biology, Boekelheide said, is active and interactive, with lots of moving parts and a resulting complexity. Eventually, however, further scientific advances will allow the process to become simpler. “But we will have the simplicity of knowledge, rather than the simplicity of ignorance,” he said.

Systems biology is an interdisciplinary field that not only identifies biological components and their interactions, but also offers explanations for how these actions take place. Systems biology, therefore, holds the promise of predicting the toxicity of an entire group of chemicals that share similar mode-of-action pathways and mechanisms of causing toxicity.



Boekelheide is a pioneer in mixtures assessment, through his work with the Superfund Research Program Center at Brown and through a [grant](#) from NIEHS studying the effects of exposure to toxic substances in mixtures. (Photo courtesy of Steve McCaw)

Speaker Maurice Whelan, Ph.D., of the European Commission Joint Research Centre, referred indirectly to the difference between traditional and emerging risk assessment, by saying, “We spend billions generating data. We need to understand, and not just measure.”

The urgency for finding more efficient toxicity testing is perhaps greatest in Europe, where animal testing will be restricted, and animal testing of cosmetics banned, next year. Speaker Derek Knight, Ph.D., of the European Chemicals Agency, outlined the kinds of guidance being given for using nontraditional data, but noted that the European Union is still trying to get a consensus view of the challenges of using nonstandard data.

Looking at biochemical pathways and effects of mixtures

The issue is not just efficiency, but improvement of toxicity risk assessment. Whelan underscored the intricacies of the process by which substances cause a toxic response through biochemical pathways.

One hope for systems biology is that it will also allow scientists to make greater inroads into understanding the effect of mixtures of chemicals — a more realistic view of the risks to humans living in a chemical soup.

Presentations ranged from an historical view of the U.S. Environmental Protection Agency’s struggle to establish traditional risk assessment, to case studies of new risk assessment approaches.

Many present seemed to agree that emerging sciences require a greater-than-ever need for scientists from varied disciplines to work together. A second consensus was that new risk assessment approaches require a paradigm shift that will be painful and controversial, but there is no going back.

“Change,” said one attendee, “is going to happen whether we lead it or not.”

(Cindy Loose is a contract writer with the NIEHS office in Bethesda, Md.)

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NTP board supports systematic review, new carcinogen concepts

By Robin Mackar

The literature-based analysis capabilities of the National Toxicology Program (NTP) took center stage during its Board of Scientific Counselors meeting June 21-22 at NIEHS.

Ruth Lunn, Dr.P.H., director of the [Office of the Report on Carcinogens \(RoC\)](#), and her staff, were well prepared to present the board with concepts outlining the planned reviews for five substances proposed for potential inclusion in the RoC, while Kris Thayer, Ph.D., and her [Office of Health Assessment and Translation \(OHAT\)](#) team wowed the board with their plans to bring systematic review methodology and new information management tools into their literature-based evaluations.



Balbus is the chair of the Emerging Science for Environmental Health Decisions Government Liaisons. The next workshop in the series, [Exploring Human Genomic Plasticity and Environmental Stressors: Emerging Evidence on Telomeres, Copy Number Variation, and Transposons](#), will be held Oct. 4-5 in Washington, D.C. (Photo courtesy of Steve McCaw)

Systematic review will enhance transparency

“The board is very enthusiastic and supportive of the NTP taking a leadership role in systematic review,” said BSC chair David Eastmond, Ph.D., of the University of California, Berkeley, as he summarized the sentiments of the board, after hearing an engaging presentation by Thayer.

“Systematic review is a scientific investigation that focuses on a specific question, and uses explicit, prespecified methods to identify, select, summarize, and assess the findings of similar but separate studies,” Thayer explained. “It’s traditionally been used for evaluating health care interventions but, from what we’ve seen over the past year, it’s going to be a really powerful tool for conducting our literature-based evaluations and helping NTP develop evidence-based conclusions.”

Thayer stressed that a systematic review does not eliminate the need for expert judgment, nor does it guarantee reproducibility in the overall evidence-based conclusions, but she emphasized how it will enhance transparency and allow for more consistent data collection and evaluation.

A critical initial step of conducting a systematic review, she said, is to develop a protocol, or predefined approach, that outlines how the evaluation will be conducted. Thayer added that the NTP will engage technical experts, interagency partners, and members of the public, to refine the scope of an evaluation and create the systematic review protocol. Thayer finished by walking the board through a series of demonstrations of how a protocol might work from start to finish.

Board member David Dorman, D.V. M., Ph.D., of North Carolina State University, and others, applauded NTP for taking a lead role in bringing this approach to fruition and encouraged the NTP to share these tools with others. “The need for this cannot be overstated,” said new Board member Robert Chapin, Ph.D., of Pfizer. “It will be the shining jewel for the NTP.”

Further enhancing the environment of animals in NTP studies

Angela King-Herbert, D.V.M., who leads the NTP Laboratory Animal Management Group, updated the board on plans to enhance environmental enrichment



Bucher, right, and Eastmond listened intently to the discussions. (Photo courtesy of Steve McCaw)



Birnbaum clearly enjoys spending time talking toxicology with board members. She updated them on the NIEHS strategic planning process. (Photo courtesy of Steve McCaw)



Witt was well prepared to respond to questions from the board about how the NTP is planning to broaden the scope of its genetic toxicity testing contract. (Photo courtesy of Steve McCaw)

in rodent studies. King-Herbert explained how environmental enrichment seeks to enhance an animal's well-being. She said there is not a standardized approach for how this should occur. "It can include, for example, things like ensuring that the animals are socially housed and creating an environment that promotes the animal's natural behaviors."

King-Herbert said the approaches for environmental enrichment proposed by NTP are in accordance with the 2011 Guide for the Care and Use of Laboratory Animals. She discussed how the NTP will phase in two different enrichment items, including crinkled natural kraft paper and plastic rectangular shelters, and how the NTP will closely monitor the impact of the enrichment. An NTP animal welfare committee has been established to oversee these activities. The Board discussed the complexities of understanding the potential impacts of environmental enrichment on toxicity studies, but also expressed its strong support for moving forward.

Strategic plan update, green light on genetic toxicity testing

Other meeting items included an update from NIEHS/NTP Director Linda Birnbaum, Ph.D., on the nearly finalized NIEHS [strategic plan](#). "This plan will be a blueprint for the entire field of environmental health sciences," Birnbaum said.

NTP genetic toxicologist Kristine Witt received the green light from the board, which unanimously voted to approve a concept that would expand the NTP's genetic toxicity testing capabilities to include human cells. And, OHAT's Andrew Rooney, Ph.D., received praise for completion of the NTP Monograph on Health Effects of Low-level Lead.

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison.)



King-Herbert outlined plans to further enrich the environment of rodents being used in NTP studies. (Photo courtesy of Steve McCaw)

Report on Carcinogens process in action

As part of the [new process](#) for preparing the RoC, Lunn and her staff presented the board with five draft concepts on substances being considered for review for possible listing in future editions of the RoC. The five substances — 1-bromopropane, cumene, ortho-toluidine, pentachlorophenol and trichloroethylene — came from a longer list of 15 [nominated substances](#) that received input from the public in January. Each draft concept outlined the rationale for the nomination and the NTP's approach for conducting the cancer evaluation. A web page will be developed and continuously updated for each substance reviewed.

The board reviewed and commented on each draft that outlined the NTP's proposed evaluation strategy that may vary depending on the complexity of the scientific information on the substance.

Birnbaum and NTP Associate Director John Bucher, Ph.D., thanked the board members for their valuable input. Birnbaum will make the final decision this summer on the substances that will be developed into monographs and proceed through the RoC evaluation process.

Bucher emphasized to the board how the NTP has improved the RoC process. "The NTP monograph developed for each substance that undergoes study will clearly show how we reached our conclusions. It will be a more transparent process."



Board member Richard Miller, D.V.M., Ph.D., of GlaxoSmithKline, provided valuable input on a wide range of topics covered at the NTP meeting, including serving as a reviewer for the pentachlorophenol draft concept for the RoC. (Photo courtesy of Steve McCaw)



Lunn outlined the process for the preparation of the RoC. Lunn and her staff, including Gloria Jahnke, Ph.D., and Diane Spencer, presented the board with five draft concepts for consideration. (Photo courtesy of Steve McCaw)



NTP toxicologist Michelle Hooth, Ph.D., succinctly updated the board on the seven technical reports that were approved by a panel of external experts in February. See story for more details. (Photo courtesy of Steve McCaw)



Thayer enjoyed a positive reception for her update on how NTP is bringing systematic review to fruition in literature-based evaluations. (Photo courtesy of Steve McCaw)



New NTP board member Chapin was at home at NIEHS and was very supportive of the presentation on systematic review. (Photo courtesy of Steve McCaw)



Rooney is all smiles, now that the NTP low-level lead evaluation is completed. (Photo courtesy of Steve McCaw)

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This month in EHP

This month's feature stories in [Environmental Health Perspectives \(EHP\)](#) tackle the timely issues of fracking and replacements for toxic chemicals.



<http://twitter.com/ehponline>

Focus — The Future of Fracking: New Rules Target Air Emissions for Cleaner Natural Gas Production

Natural gas is lauded as a cleaner-burning fuel than either coal or oil, but getting the fuel out of the ground can be a dirty process, especially given the widespread adoption of the technology known as hydraulic fracturing or fracking. Concerns about toxic air emissions, from previously unregulated fracking sites, led to the U.S. Environmental Protection Agency announcement April 18 of new and updated air pollution regulations for these facilities, as well as certain other elements of oil and natural gas production and transmission. Compliance with the new regulations is expected to result in major reductions in emissions of methane and volatile organic compounds, particularly from newly fracked natural gas wells.



Spheres of Influence — Why Is It So Difficult to Choose Safer Alternatives for Hazardous Chemicals?

The discovery of persistent, bioaccumulative, and toxic flame-retardant chemicals everywhere, from animals north of the Arctic Circle to the breast milk of California women, has been a cause for considerable concern. Alternative flame retardants were introduced to replace these chemicals, but investigators had not even produced the first empirical data on the substitutes' metabolic fate and toxicity, before emerging evidence indicated they, like their predecessors, were accumulating rapidly in the environment. As the post-market research continues, some are wondering, who, exactly, decides on the replacements for toxic chemicals and on the basis of what criteria; and why does finding truly safer alternatives seem so difficult.

Podcast with Bruce Blumberg — What Do We Know About Obesogens?

Human beings, as a species, are putting on weight. Obesity rates are rising in rich and poor countries alike, for a variety of reasons, from changing dietary habits and activity levels, to exposure to artificial nighttime light. Mounting evidence, from over the past decade, suggests that certain chemicals may be playing a role as well. For some people, so-called obesogens may be altering their metabolism and fat cell development, making it harder to maintain a healthy weight. In this month's [Researcher's Perspective](#) podcast, host Ashley Ahearn talks with NIEHS grantee Bruce Blumberg, Ph.D., about the state of our understanding of obesogens.

Featured commentaries, reviews, and research this month include the following:

- Information Quality in Regulatory Decision Making
- Household Sprays and Heart Rate Variability
- Using Biosensor Zebrafish to Identify Estrogen Targets
- Autism and Maternal Smoking During Pregnancy

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Extramural papers of the month

By *Nancy Lamontagne*

- [Gene variants linked with faster Parkinson's disease progression](#)
- [Cardiovascular effects of Beijing Olympics air pollution reduction](#)
- [Environmental exposures influence behavior of later generations](#)
- [Semiconducting properties of nanoparticles linked with oxidative damage](#)



Read the current Superfund Research Program [Research Brief](#). New issues are published on the first Wednesday of each month.

Gene variants linked with faster Parkinson's disease progression

NIEHS grantees report that Parkinson's disease patients with two specific variants of the alpha-synuclein (SNCA) gene progressed toward motor decline significantly faster than patients without these variants. This work could lead to new therapies and help identify those who would benefit most from early intervention.

The researchers followed 233 well-characterized Parkinson's disease patients in central California, for an average of 5.1 years, and found that carriers of the Rep1 263bp variant of the SNCA gene had a four-fold higher risk of faster motor decline. Patients with both the Rep1 263bp promoter and rs356165 variants had an even stronger trend in progression toward motor decline.

Although the findings need replication in other well-characterized Parkinson's disease populations, the researchers say that their work shows that these gene variants could be used to identify patients who will likely experience faster disease progression. The work also points to the alpha-synuclein pathway as a promising potential therapeutic target.

Citation: [Ritz B](#), [Rhodes SL](#), [Bordelon Y](#), [Bronstein J](#). 2012. Alpha-synuclein genetic variants predict faster motor symptom progression in idiopathic Parkinson disease. PLoS One 7(5):e36199.

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Cardiovascular effects of Beijing Olympics air pollution reduction

The Chinese government shut down factories and limited automobile traffic during the Beijing Olympics, to lessen air pollution. These temporary changes in air pollution levels were associated with acute changes in cardiovascular biomarkers in healthy young people, according to a new study from NIEHS grantees. The research adds evidence that higher levels of air pollution are linked with an increased risk of cardiovascular problems.

The researchers recruited 125 male and female resident doctors, who worked at a central Beijing hospital, to participate in the study. Participants had never smoked, were free of disease, and had an average age of 24. They visited the clinic before the air pollution controls were in place, while the pollution controls were used, and after the games had ended.

During the Olympics, the study participants showed significant reductions in von Willebrand factor and soluble CD62P levels, which are both associated with blood coagulation. Soluble CD62P and systolic blood pressure levels increased significantly once the pollution controls were lifted after the Olympics.

Citation: Rich DQ, Kipen HM, Huang W, Wang G, Wang Y, Zhu P, Ohman-Strickland P, Hu M, Philipp C, Diehl SR, Lu SE, Tong J, Gong J, Thomas D, Zhu T, Zhang JJ. 2012. Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. JAMA 307(19):2068-2078.

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Environmental exposures influence behavior of later generations

A new NIEHS-funded study shows that animals whose ancestors were exposed to a fungicide have a more profound reaction to stress than the offspring of unexposed animals. The work demonstrates that an ancestor's exposure can influence the stress response of future generations.

The authors of the study used a systems biology approach by examining genetic and molecular changes in the brain as well as behavior. They exposed gestating female rats to the fungicide vinclozolin and later performed testing on the third generation of offspring. The third generation offspring from the exposed rats showed differences in physiology and metabolic activity compared to descendants of unexposed rats. When exposed to stress during adolescence, the offspring of exposed rats had greater anxiety, sensitivity to stress, and more activity in stress-related regions of the brain.

Citation: Crews D, Gillette R, Scarpino SV, Manikkam M, Savenkova MI, Skinner MK. 2012. Epigenetic transgenerational inheritance of altered stress responses. Proc Natl Acad Sci U S A 109(23):9143-9148.

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Semiconducting properties of nanoparticles linked with oxidative damage

An NIEHS grantee and his colleagues used the semiconducting properties of metal oxide nanoparticles to quickly identify nanoparticles that could cause toxicity *in vitro* and *in vivo*. This new method could speed assessment of emerging new nanomaterials and prioritize materials for further study.

The researchers first predicted which of 24 metal oxide nanoparticles might cause cell injury, based on semiconducting properties, and then analyzed all the nanoparticles with a high-throughput assay that assessed oxidative damage to a variety of cell types. In only a few hours, the screen identified oxidative damage from six nanoparticles — the same ones that previously met the researchers' predictive criteria. Animal tests of the 24 metal oxide nanoparticles showed that the same six caused lung inflammation.

Citation: Zhang H, Ji Z, Xia T, Meng H, Low-Kam C, Liu R, Pokhrel S, Lin S, Wang X, Liao YP, Wang M, Li L, Rallo R, Damoiseaux R, Telesca D, Madler L, Cohen Y, Zink JI, Nel AE. 2012. Use of metal oxide nanoparticle band gap to develop a predictive paradigm for oxidative stress and acute pulmonary inflammation. ACS Nano 6(5):4349-4368.

(Nancy Lamontagne is a science writer with MDB, Inc., a contractor for the NIEHS Division of Extramural Research and Training, Superfund Research Program, and Worker Education and Training Program.)

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Intramural papers of the month

By Anshul Pandya, Sonika Patial, Sheetal Thakur, and Sheila Yong

- [Pol II pausing modulates basal gene expression in signal transduction cascades](#)
- [Clustered mutations attributed to body's natural defenses](#)
- [STAT6 and LRP1 polymorphisms are associated with food allergen sensitization in Mexican children](#)
- [Socioeconomic adversity in early life impacts the future risk of rheumatoid arthritis](#)

Pol II pausing modulates basal gene expression in signal transduction cascades

NIEHS scientists have revealed that RNA polymerase II (Pol II) pausing does not necessarily lead to higher gene expression upon induction of stimulus-responsive networks. Rather, it is important in modulating basal gene expression. The research offers a new model for understanding how paused Pol II impacts gene expression in resting cells.

Using the systems biology approach in *Drosophila* S2 cells and focusing primarily on the immune response pathways, they found that many downstream target genes were rapidly induced, despite not harboring paused Pol II at their promoters prior to pathogenic challenge. Instead, they observed a higher prevalence of Pol II pausing at promoters of genes whose expression levels were more modest. Genes in the latter category encode regulatory components and receptor ligands that either initiate or dampen the signaling cascade.

The scientists also knocked down the expression of NELF, a component required for Pol II pausing, and found that the magnitude of the overall immune response was diminished, regardless of whether the genes experienced Pol II pausing or not. Their findings indicate that, although the regulatory components are more modestly expressed in response to immune challenge, their basal expression in resting cells is more tightly regulated so that these cells are better poised to rapidly initiate the immune response cascade as needed. (SY)

Citation: [Gilchrist DA, Fromm G, dos Santos G, Pham LN, McDaniel IE, Burkholder A, Fargo DC, Adelman K. 2012. Regulating the regulators: the pervasive effects of Pol II pausing on stimulus-responsive gene networks. Genes Dev 26\(9\):933-944.](#)

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Clustered mutations attributed to body's natural defenses

A collaborative team, comprised of scientists from NIEHS, The Broad Institute, and the University of North Carolina at Chapel Hill, has identified DNA regions with a high number of nonrandom mutations in yeast and some human cancers. The findings may represent one of the mechanisms of cancer development.

Researchers subjected yeast cells to the DNA damaging agent methyl methanesulfonate and then sequenced the genomes. They found that certain patches of DNA sequence contained clusters with more mutations than

in the rest of the genome. The data challenged the traditionally held view that mutations occur randomly. Further analysis suggested that these mutations occurred at the same time in stretches of abnormally long single-stranded DNA.

The research team developed bioinformatics tools to determine if human cancers contained similar mutation clusters and, surprisingly, nearly half of them did. These mutations, however, were not caused by environmental damage, but by a specific set of proteins known as APOBEC cytosine-deaminases. APOBEC proteins, which are part of the human immune system, attack viruses that enter the body.

The results of this study suggest that several antiviral drugs, capable of stimulating APOBEC genes, should be considered potential mutagens as they relate to mutation clusters. **(SP)**

Citation: Roberts SA, Sterling J, Thompson C, Harris S, Mav D, Shah R, Klimczak LJ, Kryukov GV, Malc E, Mieczkowski PA, Resnick MA, Gordenin DA. 2012. Clustered mutations in yeast and in human cancers can arise from damaged long single-strand DNA regions. *Mol Cell* 46(4):424-435. [Story](#)

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STAT6 and LRP1 polymorphisms are associated with food allergen sensitization in Mexican children

A new study, conducted by NIEHS scientists, provides evidence that the polymorphisms in *STAT6*, signal transducer and activator of transcription-6, and *LRP1*, low-density lipoprotein receptor-related protein-1, genes are associated with sensitization to food allergens in asthmatic patients. Asthmatic patients are at increased risk for sensitization to food allergens, so the results may not be completely generalizable to the entire population.

Prior to the publication of this paper, epidemiologists had identified family history as a risk factor for food allergies, but no genetic variants had been conclusively identified for food sensitization or clinical food allergies. Therefore, the research team examined the associations between food allergen sensitization and single nucleotide polymorphisms (SNPs) in five autosomal candidate genes: *CD14*, *IL10*, *IL13*, *SPINK5*, and *STAT6*.

The study included 162 asthmatic children from the Mexico City Childhood Asthma Study, who tested positive to at least one food allergen using skin prick tests, and their parents, using the case-parent triad design. The research team found that several SNPs in or near *STAT6*, and two more in the nearby *LRP1* gene, were associated with sensitization to food allergens. **(AP)**

Citation: Hancock DB, Romieu I, Chiu GY, Sienra-Monge JJ, Li H, Estela Del Rio-Navarro B, London SJ. 2012. STAT6 and LRP1 polymorphisms are associated with food allergen sensitization in Mexican children. *J Allergy Clin Immunol* 129(6):1673-1676.

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Socioeconomic adversity in early life impacts the future risk of rheumatoid arthritis

Epidemiologists from NIEHS report that women with lower childhood socioeconomic status are more likely to develop rheumatoid arthritis (RA) in adulthood. The study is the first to describe an association of multiple childhood socioeconomic factors, such as household education, income, and maternal age, with adult onset RA.

The researchers analyzed information from more than 50,000 women aged 35-74 from the NIEHS Sister Study cohort. Participants were asked about perinatal factors, demographics, residential history, lifestyle, medical history, and medication use. The study showed that women who were raised in a household with lower education, lower income, food insecurity, and young maternal age were at higher risk of developing RA as adults. The impact of childhood socioeconomic adversity on RA was the most apparent in women with lower adult educational attainment. Women with fathers who smoked three months prior to conception also had a higher risk of RA, regardless of socioeconomic factors.

These emerging results are an important step toward investigating the role of developmental, environmental, and social factors on the risk for RA in women. **(ST)**

Citation: [Parks CG](#), [D'Aloisio AA](#), [DeRoo LA](#), [Huiber K](#), [Rider LG](#), [Miller FW](#), [Sandler DP](#). 2012. Childhood socioeconomic factors and perinatal characteristics influence development of rheumatoid arthritis in adulthood. *Ann Rheum Dis*; doi:10.1136/annrheumdis-2011-201083 [Online 14 May 2012].

(Anshul Pandya, Ph.D., is an Intramural Research Training Award [IRTA] fellow in the NIEHS Laboratory of Neurobiology. Sonika Patial, D.V.M., Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction. Sheetal Thakur, Ph.D., is an IRTA fellow in the NTP Toxicology Branch. Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction.)

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Inside the Institute

Zeldin welcomes 2012 summer interns to NIEHS

By Ian Thomas

High school and college students from across the country gathered in Rodbell Auditorium for the June 14 kickoff of the 2012 [NIH Summer Internship Program](#) at NIEHS, which runs from May until August. Led by Scientific Director [Darryl Zeldin, M.D.](#), the meeting provided participants with a snapshot of what to expect from their time at the Institute, followed by a lengthy question and answer session about the program.

“Over the next several weeks, you’re going to experience a lot, so don’t be shy about asking questions,” said Zeldin, who opened his talk with a handful of entertaining photographs from his high school and college days. “Ultimately, your time here will be what you make of it, so be proactive with your mentors and get involved in everything that you can.”

A plethora of experiences

Throughout the summer, students will work alongside many of the top researchers and staff at NIEHS, contributing to projects and conducting lab work as part of a comprehensive, hands-on learning curriculum. During their time at NIEHS, interns have the option of focusing on any number of environmental health specialties, such as DNA repair, cancer biology, bioinformatics, or clinical research.

“I can’t wait to get started,” said Hannah Leker, a public health major at the University of North Carolina at Chapel Hill. “At this point in my career, I haven’t completely decided on which direction I want to go, so the chance to get involved in a little of this and a little of that is really exciting.”

This notion of branching out into a variety of different areas proved to be a major theme of the morning, as pointed out by Zeldin.

“Between now and the fall, you’ll be exposed to everything from bench work in a lab to clinical research, some of it you’ll like and some of it you won’t,” said Zeldin, who elaborated on some of the pros and cons of an M.D. versus a Ph.D., as well as the types of career paths that are associated with each. “The hope is that, by the time you leave here, you’ll have a much clearer idea of where you want to focus your studies going forward.”



As he talked about the summer internship experience, Zeldin reminisced about his own path from a young and curious student to the top scientific leadership post in the NIEHS Division of Intramural Research. (Photo courtesy of Steve McCaw)



The students begin their internships in May or June, depending on when their school years end. For some of the interns, the summer project can lead to a publication or a presentation at a professional meeting. (Photo courtesy of Steve McCaw)

As in past years, the high point of the program will be the end-of-summer poster session July 26, when students get to show off what they've learned during their time in the lab, which could potentially lead to a publication or presentation at a professional meeting.

Taking time

At the end of the talk, Zeldin reminded the students that while it's important to be proactive, it's equally as important to take one's time, both during the internship and beyond.

"Environmental health isn't going anywhere," said Zeldin. "Take your time in school and find that one specific area of the field that most excites you, then build your career on it. Do that and you'll be both happy and successful as a scientist."

(Ian Thomas is a public affairs specialist with the NIEHS Office of Communications and Public Liaison, and a regular contributor to the Environmental Factor.)

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Career exploration panel gives advice to summer interns

By Ian Thomas

Participants in this year's [NIH Summer Internship Program](#) at NIEHS attended a question and answer style career panel meeting comprised of five of environmental health's brightest minds June 19. Featuring representatives from NIEHS, the University of North Carolina at Chapel Hill (UNC), and the University of Maryland (UMD), the panel treated attendees to stories of what it means to build a career in public health, while offering them the chance to ask questions on everything from degree programs to mentorships.

"Regardless of the career, there's no substitute for experience to help you decide on a field," said [Perry Blackshear, M.D., Ph.D.](#), head of the NIEHS Polypeptide Hormone Action Group, who encouraged students to be proactive during their time at the Institute and beyond. "If you think you want to do research, get involved in a lab. If you want to work in medicine, volunteer with a clinic and see if you like working with patients. Whatever the interest, take advantage of the chance to learn about it firsthand."



The interns enjoyed the rare opportunity to learn about the personal history of a variety of people in a range of biomedical careers, and several took advantage of the informal question and answer format of the event. (Photo courtesy of Steve McCaw)

Many roads, same destination

One major topic of discussion during the session was the notion that science is a diverse field, comprised of countless career paths, specialties, and degrees, not all of which are for everyone. This point was reflected in the diverse backgrounds of the panelists themselves.

“I actually began my career in biology, thinking I wanted to go to vet school,” said [Erin Hopper, Ph.D.](#), director of training initiatives in biomedical and biological sciences at UNC and a former postdoc at NIEHS ([see story](#)). “Even after I changed my major to chemistry and earned my Ph.D., I was still interested in a career away from the bench. However, it wasn’t until I got to NIEHS and started getting involved with people that I found my way into what I do now in career development.”

Remembering the basics

While degrees and programs of study will be among the major decisions students will make in the years to come, the panelists agreed that they shouldn’t lose sight of the little things when preparing for a career in science.

“No matter what you choose to do for a living, take the time to learn to read, write, and speak effectively,” said [William Higgins, Ph.D.](#), of the UMD biology department. “So many of our students today don’t spend enough time developing these simplest of skills, and they’re absolutely vital to success in any field, public health included.”

The value of role models

As many of these students continue to explore their options for potential careers, the panelists told the interns that surrounding themselves with the right people is crucial to the process. Nowhere is that more important than in the selection of a mentor.

“Be as selective about choosing your mentor as they are about choosing you,” noted Blackshear. “Different people mentor in different ways, just as different people learn in different ways. Find one that best matches who you are and get to know them.”

“Whether it’s your mentors, your teachers, or your friends, surround yourselves with people who excel at what they do and take notes,” added Higgins. “Learning what makes them successful and integrating that into how you build your own career could one day take you to similar heights.”

(Ian Thomas is a public affairs specialist for the NIEHS Office of Communications and Public Liaison, and a regular contributor to the Environmental Factor.)



Blackshear was the first panelist to describe his career path, which took him to a traditional academic research career before landing him at NIEHS. Blackshear has held several leadership positions at the Institute, including director of clinical research, acting scientific director, and his current role as head of the NIEHS Polypeptide Hormone Action Group. (Photo courtesy of Steve McCaw)



Young women in the audience could relate to Dudek, above, and Hopper, who have combined career and family in a field that is only beginning to reflect the gender balance of the general population. Dudek obtained tenure in 2010, overcoming the biggest single obstacle in the career of a young researcher ([see story](#)). (Photo courtesy of Steve McCaw)

NIH Summer Internship Career panel

Perry Blackshear, M.D., Ph.D.

Lead researcher
NIEHS Polypeptide Hormone Action Group

Serena Dudek, Ph.D.

Lead researcher
NIEHS Synaptic and Developmental Plasticity
Group

David Kurtz, D.V.M., Ph.D.

Veterinary staff scientist
NIEHS Comparative Medicine Branch

Erin Hopper, Ph.D.

Assistant director of the UNC Academic and
Career Excellence Program

William Higgins, Ph.D.

Associate professor
UMD College of Computer, Mathematical, and
Natural Sciences



Kurtz, left, and Hopper, center, laughed as Higgins mixed his iconoclastic wit with solid advice about career preparation. People skills are critical, he told the students, because science is a collaborative effort, not a solitary, ivory tower endeavor. Scientists need to communicate, persuade, and manage people who may not answer to them. (Photo courtesy of Steve McCaw)

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